

THE CLINICAL SIGNIFICANCE OF DEVELOPMENTAL DENTAL ANOMALIES

by

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STATEMENT OF AUTHENTICITY

The work presented in the thesis is, to the best of the candidate's knowledge and belief, original, except as acknowledged in the text, and the material has not been submitted, either in whole or in part, for a degree at this or any other university.

A handwritten signature in black ink, appearing to read 'W. Kim Seow', with a stylized, sweeping flourish at the end.

W. KIM SEOW

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PUBLICATIONS FROM THE THESIS

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3. Seow WK, Humphrys C, Mahanonda R, Tudehope DI (1988). Dental eruption in low birth-weight, prematurely-born children: A controlled study. Pediatric Dentistry 10: 39-42.

4. Seow WK, Latham SC (1986). The spectrum of dental manifestations in vitamin D-resistant rickets. Pediatric Dentistry 8: 245-250.

5. Seow WK, Romaniuk K, Sclavos S (1989). Micromorphologic analysis of dentin in vitamin D-resistant rickets: correlation with clinical findings. Pediatric Dentistry 11: 203-208.

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6. Lai PY, Seow WK (1989). A controlled study of the association of various dental anomalies with hypodontia. *Pediatric Dentistry* 11: 291-295.
7. Seow WK, Lai PY (1989). Association of taurodontism with hypodontia: a controlled study. *Pediatric Dentistry* 11: 214-218.
8. Seow WK (1989). Palmoplantar hyperkeratosis with short stature, facial dysmorphism, and hypodontia: a new syndrome? *Pediatric Dentistry* 11: 145-149.
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ABSTRACT

This thesis studied 3 broad groups of developmental dental anomalies commonly encountered in paediatric dentistry. Firstly, enamel hypoplasia in prematurely-born children was investigated as a representative example of developmental defects of enamel. Secondly, the dentitions of patients with vitamin D resistant-rickets were studied to explore the clinical significance of developmental defects of dentine. Thirdly, developmental defects of number and morphology were examined by investigations of hypodontia and other dental anomalies associated with it. In addition, the prevalence of furcation accessory canals in primary molars was also studied.

The work in this thesis was organised into a series of publications which are summarised below.

In the controlled studies of prematurely-born children it was shown that the prevalence of enamel defects increased with decreasing birth weight. In the very low birthweight (VLBW, <1500 g) children, the prevalence was 62.3 percent compared to 27.3 percent in the low birthweight (LBW 1500-2500 g) group. In children with normal birthweight (NBW) of >2500 g, the prevalence was 12.8 percent.

A systemic factor which may play a central role in the pathogenesis of the enamel defects is mineral deficiency or osteopenia which is diagnosed as radiological demineralization of

the long bones. A comparison of the radiological cortical area of the humerus in 31 VLBW children with enamel hypoplasia and 14 VLBW children without enamel hypoplasia showed that the group with enamel hypoplasia had a lower mean cortical area of $10.1 \pm 1.9 \text{ mm}^2$ compared with $13.9 \pm 1.4 \text{ mm}^2$ in children without enamel hypoplasia, indicating that severe osteopenia is associated with enamel hypoplasia. In addition to systemic factors, local trauma from the laryngoscope during endotracheal intubation also contributes to the aetiology of enamel defects. It was shown in this thesis that intubated children frequently suffered localised enamel defects which were usually found on the maxillary left anterior teeth.

Dental eruption was also investigated in prematurely-born children in a controlled study to determine if it was affected by low birth weight and birth prematurity. The data were analysed using chronological and corrected (true biological) ages of the prematurely-born group. The results showed that when chronological ages of the children were used, VLBW children have significant retardation of dental eruption compared with LBW and NBW children, particularly before 24 months of age. However, when corrected ages of the VLBW children were used, no significant differences could be detected, indicating that the "delay" in dental eruption may be due simply to their early birth.

In the studies of vitamin D-resistant rickets (VDRR), the analysis of 13 affected patients indicated that the dental manifestations occurred in a wide spectrum of severity which was determined by several factors such as hereditary, sex and medical

treatment. A grading system of the spectrum of dental manifestations is introduced as follows. Grade I includes near-normal dentition, while Grade II indicates involvement of only a few teeth and Grade III shows greatly enlarged pulp chambers, multiple dental abscesses, and poorly calcified dentine. These clinical grades were correlated with histological findings in a further study which showed that Grade I teeth had globular dentine which constituted less than half of the total dentine thickness, and Grade II teeth had globular dentine involving more than half but not the entire dentine thickness. In Grade III teeth, globular dentine extended throughout the entire thickness of dentine. A clinical grading system is invaluable in determining the risk of an affected patient to develop dental complications. Strategies are available for the prevention of dental abscesses in each grade of severity and should be used appropriately.

Hypodontia or agenesis of the teeth was studied in relation to other dental anomalies commonly occurring with it. Ankylosis of primary molars was the most significant associated anomaly, being found in 65.7 percent of patients with hypodontia compared with only 1.5 percent of matched, control patients. Taurodontism which is a tendency for the body of a tooth to enlarge at the expense of the roots, was observed in 34.3 percent of hypodontia compared to 7.1 percent of the controls. Other dental anomalies significantly associated with hypodontia include enamel hypoplasia (11.9 percent) and conical incisors (8.9 percent). The diagnosis of taurodontism in the mandibular first permanent molar from panoramic radiographs was established in a separate study, using a novel biometric method.

In addition, a new syndrome in a family showing palmoplantar hyperkeratosis, short stature, facial dysmorphism, hypodontia and taurodontism was described to illustrate the importance of dental anomalies in the diagnosis of medical syndromes.

The prevalence of accessory furcation canals was also investigated as part of the studies on anomalies of dental morphology. ⁿSeventy-five primary molars were studied using a dye penetration technique under vacuum suction. It was shown that 42.7 percent of these molars had foramina located within the furcation region. This high prevalence indicates the need for greater clinical consideration during endodontic and periodontal management of primary molars.

The final chapter of the thesis discusses the above studies in the light of current understanding of the clinical significance of these dental anomalies.

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CHAPTER ONE

REVIEW OF THE LITERATURE

REVIEW OF THE LITERATURE

General Introduction

Despite the persistence of some entities of dental caries (Seow, 1987; Sclavos, Porter and Seow, 1989), the prevalence of dental decay has declined in recent years (Bohannon, 1982; Burt, 1985). Hence, the clinical practice of paediatric dentistry is now focussed on other problems. Current clinical problems gaining increasing recognition include developmental dental anomalies which exist in a diverse panorama of aberrations of tooth number, size, form, structure and eruption. These abnormalities may present significant clinical problems of aesthetics and malocclusion, as well as predisposition to dental decay and pulpal abscesses (Seow, 1984a, Gorlin et al, 1978; Nikiforuk and Fraser, 1979). However, the pathogenesis and clinical implications of many developmental dental anomalies are not well understood. In particular, the increasing sophistication of paediatric medical care in recent years has resulted in children born with severe medical conditions surviving to adulthood. The study of dental anomalies accompanying many of these conditions may provide significant insight into possible pathogenetic mechanisms involved as well as their dental management. *Refs.*

Yet, few clinical studies are available. *o)*

Due to the constraints of available clinical material, this thesis aims to study only a representative sample of the diverse manifestations of developmental dental anomalies to provide further insight into the clinical significance of these conditions. The first chapter reviews the relevant literature. The next three chapters investigate examples of developmental enamel defects which are found in prematurely-born children, a group particularly prone to develop the condition. In these chapters, the prevalence of dental defects as well as possible aetiological factors are discussed.

In the next two chapters, an inherited disorder, vitamin D-resistant rickets, is studied with respect to the diagnosis and clinical management of the broad spectrum of dental manifestations of the condition.

The last four experimental chapters address problems related to abnormalities of tooth number and form, as well as aberrant openings in the furcation region of primary molars. In addition, the importance of dental features in the diagnosis of dysmorphic syndromes is recognised in the study of a family affected by a new syndrome previously undescribed.

Finally, the last chapter of the thesis discusses all the findings of the investigations in the light of current understanding of the pathogenesis and clinical implications of the various types of dental anomalies.

Normal Dental Development

Introduction

Embryonic development of human teeth (ontogeny) reflects a phylogenetic history first observed in primitive fishes which adapted dermal denticles from ectodermally-derived scales overlying the jaws (Stewart et al, 1982). In humans, enamel of teeth is derived from ectoderm while the anlagen for dentine, pulp and periodontal tissues is provided by neural crest ectomesenchyme.

The process of tooth formation can be conveniently divided into the following descriptive developmental stages: initiation or bud stage, proliferation or cap stage, histodifferentiation or bell stage, morphodifferentiation, apposition, mineralization and eruption (Ten Cate, 1985). In these developmental stages, dynamic interplay of hereditary and environmental factors occurs, although the extent to which each of these influences normal and pathological development is currently unclear. Problems during the initiation and proliferation stages may produce anomalies of tooth shape or number, whereas insults during mineralization result in enamel or dentine calcification defects.

Initiation and proliferation

Ectomesenchyme derived from the neural crest provides the induction factor in odontogenesis (Slavkin, 1979). The earliest

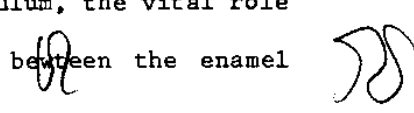
cell interactions controlling the determination of dental mesenchyme have probably already taken place during the migration of neural crest cells (Thesleff & Hurmerinta, 1981). The dental lamina, consisting of primary odontogenic tissues may be identified as early as the twenty-eighth day post-conception as an epithelial thickening at the lateral margins of the stomodeum (Osborn & Ten Cate, 1983). It proliferates into the underlying mesenchyme at specific locations to form the dental or enamel organs. The first of these to appear are the mandibular primary incisors and initiation of the entire primary dentition occurs during the second month in-utero (Kraus & Jordan, 1965). However, the factors controlling the definitive sites of tooth buds have not been established (Thesleff & Hurmerinta, 1981).

The form of the tooth is established by morphogenetic movements of the tissues. The epithelio-mesenchymal interface undergoes folding to establish the cuspal pattern of the tooth. Epithelial morphogenesis appears to be under the influence of mesenchymal tissue (Kollar & Baird, 1970; Kollar & Fisher, 1980).

Histodifferentiation

A series of cellular changes result in the formation of four distinct layers surrounding the ectomesenchyme. These are the inner enamel epithelium, the stellate reticulum, the stratum intermedium, and the outer enamel epithelium (Provenza, 1986). Each of these cellular layers has an important function in the

development of the enamel organ. The inner enamel epithelium differentiates to form ameloblasts which are involved in enamel formation, while the stellate reticulum and stratum intermedium provide support and nutrition for enamel formation (Osborn & Ten Cate, 1983). The outer enamel epithelium has, in addition to its passive role of containing the stellate reticulum, the vital role of controlling the exchange of substances between the enamel organ and its environment (Provenza, 1986).



The formation of enamel and dentine involves the differentiation of specialised cellular layers producing matrices which are subsequently mineralized with hydroxyapatite and other minerals. Prior to enamel matrix formation, the ameloblasts exert an inductive influence on adjacent mesenchymal cells to differentiate to preodontoblasts, the precursors of dentine-forming cells (Osborn & Ten Cate, 1983).

Only when the preodontoblasts have differentiated into odontoblasts and established contact with ameloblasts of the inner dental epithelium does initiation of enamel and dentine matrix formation occur. According to Stewart et al (1982), the process consists of the following steps. Firstly, odontoblasts begin secretion of the predentine matrix between themselves and ameloblasts. Secondly, matrix vesicles from these preodontoblasts are apposed with the preameloblasts basement cell membrane and appear to alter it, stimulating secretion of enamel matrix by


ameloblasts. Thirdly, odontoblasts produce dentine matrix simultaneously with events in the second step.

The tissue interactions that control odontoblast and ameloblast cell differentiation have been studied in numerous transplantation and in-vitro studies (Slavkin et al, 1968; 1989; Thesleff, 1976;) These studies have indicated that the transmission of instructive signals to effect odontoblast and ameloblast differentiation may be matrix-mediated or cell-mediated (Thesleff & Hurmerinta, 1981).

Amelogenesis

Morphologic Events

Enamel formation is a complex process which may be divided into three stages (Weinstock, 1972). The first stage is formative, in which an organic matrix is secreted by the cells differentiated from the internal dental epithelium. This matrix is almost instantly mineralized, and the inorganic material (apatite) comprises ~~of~~ approximately 15 percent of the volume of enamel (Ten Cate, 1985). The second stage is a maturation stage which consists of further growth of mineral crystals and loss of protein and water. The third stage in enamel formation results in the addition of still more mineral and the loss of porosity (Ten Cate, 1985).



Ultrastructural studies reflect the events in amelogenesis. When the cells of the internal dental epithelium differentiate into ameloblasts, they elongate and become highly polarised, with the majority of their organelles situated in the cell body distal to the nucleus. Adjacent ameloblasts are closely approximated with the development of functional complexes encircling the cells at the distal and proximal extremities (Warshawsky, 1978). The basement lamina supporting the ameloblasts disintegrates after the onset of dentinogenesis and before the onset of amelogenesis.

In the secretory stage, synthesis of enamel proteins occur in the rough endoplasmic reticulum from which they are passed to the Golgi complex where they are packaged into membrane-bound secretory granules. These granules migrate to the distal portions of the cells and their contents released against the newly-formed mantle dentine (Simmelink, 1982). Inorganic crystals appear almost immediately after the secretion of enamel protein and some of ^{ee} ~~this~~ ^{KN} first-formed crystals interdigitate with those of dentine (Robinson et al, 1983).

The first-formed enamel is structureless, but as the ameloblasts migrate away, each cell develops a conical Tomes' process which is distinct from other parts of the cytoplasm in that it contains numerous secretory granules and small vesicles (Skobe, 1976). Protein secretion occurs in the Tomes' process at its distal end as well as its proximal region where adjacent processes meet. The secretion at the proximal extremity precedes

that at the distal extremity so that walled pits occupied by the distal end of the processes are formed (Ten Cate, 1985). Secretion from one surface of the Tomes' process then fill in the pits. There is general agreement that the enamel rods in a variety of species develop as a result of the shape and secretory pattern of the Tomes' process of the ameloblast (Simmelink, 1982).

The maturation stage of enamel formation occurs when the full thickness of enamel has been reached. This stage is preceded by programmed death of about 25 percent of ameloblasts while the viable cells begin to resemble resorptive epithelia found in other tissues (Warshawsky, 1984). Removal of protein and water and an increase in mineral content occur in the maturation stage. Although the enamel organ has been thought to be actively involved in these events (Smith, 1979) direct evidence is not available (Warshawsky, 1984).

The events that occur in the process of enamel mineralization during the maturation stage have been studied by many investigators using microradiography, polarized light microscopy, tetracycline labelling and/or autoradiography (Suga, 1983; Wennberg and Bawden, 1978; Hammerstrom, 1967). Although some investigators have proposed progressive mineralization of developing enamel as a continuous process (Leblond & Warshawsky, 1979), others have suggested that the mineralization process is accomplished in at least two distinct stages, (i) the stage of

matrix formation and (ii) the stage of maturation (Wennberg & Bawden, 1978; Suga, 1983; Reith & Boyde, 1985).

These stages have been observed in human deciduous enamel (Robinson et al, 1981; Deutsch & Gedalia, 1980; Deutsch & Peer, 1982). Early enamel mineralization has been shown to be dependent upon an intact calmodulin-regulated, calcium-transporting ATPase in secretory ameloblasts (Sasaki & Garant, 1987). However, progressive crystal growth during enamel maturation may depend on simple diffusion of minerals across the enamel organ without the involvement of active cellular calcium transport (Sasaki et al, 1987).

Enamel Proteins

During amelogenesis, the protein matrix of enamel comprises a complex mixture of components which change continuously throughout the development of enamel. Two broad groups of developing enamel proteins may be characterised based on amino acid composition: (1) amelogenins which are relatively basic, hydrophobic and proline-rich, with a molecular weight of about 25,000 daltons (Fincham et al, 1982; Aoba et al, 1987; Renugopalakrishnan et al, 1989), (2) enamelin which are acidic, glycosylated phosphoproteins with a molecular weight of approximately 55,000 daltons (Limeback, 1987; Zeichner-David et al, 1983).

The proportions of these two classes of enamel proteins and their constituents vary with the maturation of enamel. Initially, in the very early stage of enamel formation, proteins relatively rich in amino acids characteristic of enamelines are secreted (Deutsch and Alayoff, 1987). Gradually, the ameloblast secretion changes with the predominant proteins in the forming stage becoming those of amelogenins. During maturation, the amelogenin proteins are selectively lost, resulting in a relatively increased enamelin concentration in the maturing tissue (Fincham et al, 1982; Slavkin et al, 1988a).

In the process of enamel protein transformation, there is progressive protein degradation of higher molecular-weight matrix components, possibly by specific proteases (Fincham et al, 1983; Overall & Limeback, 1988). While the degradation products of amelogenin proteins seem to disappear, the enamel-bound enamelin degradation products appear to persist in the mature enamel.

In studies using human deciduous teeth, investigators have located the presence of amelogenins and enamelines at various stages of enamel formation (Deutsch & Alayoff, 1987; Farge et al, 1987; Zeichner-David et al, 1987), confirming the results of previous investigations in animal teeth (Glimcher et al, 1977; Termine et al, 1980).

The functions of enamel matrix proteins are not well understood but they are thought to play major roles in the

mineralization and structural organization of developing enamel. They may provide protein orientation for growing enamel apatite crystals or serve as initial nucleation sites for enamel apatite crystal formation (Slavkin et al, 1981). Furthermore, they may serve as calcium-binding glycoproteins and may be involved in the regulation and transport of calcium within the secretory ameloblasts (Robinson & Kirkham, 1984). In addition, enamel matrix proteins may provide a thixotropic gel-like structure which facilitates the formation of densely-packed, large enamel apatite crystals (Slavkin et al, 1981).

The exact roles played by amelogenins and enamelins in the above functions have not been completely elucidated. As most of the volume in developing enamel is occupied by the amelogenins, these hydrophobic moieties may be involved in the delineation of space which will ultimately be occupied by the mineral phase (Robinson & Kirkham, 1984). Although it has been suggested that removal of hydrophobic amelogenins leads to passive apatite crystal growth (Doi et al, 1984), recent evidence indicates that amelogenins may play an active role in the control of enamel mineralization through the complexing of calcium ions (Aoba et al, 1987).

The enamelins, on the other hand, appear to be more intimately associated with the mineral phase than the amelogenins. Recent studies have suggested that the enamelins may play a role in apatite crystal formation (Termine et al, 1979; Robinson et

do
A

al, 1982; Doi et al, 1984; Slavkin et al, 1988a). In addition, a possible nucleation role has been suggested for the enamelines (Slavkin et al, 1981). According to Robinson and Kirkham (1984), mineral binding sites on the linear enamelin proteins may delineate the long c-axis direction of the apatite crystallites and removal of enamelin proteins from the crystal surface may facilitate subsequent crystallization and expansion in width.

With advancement of techniques in molecular biology in recent years, the molecular aspects of enamel proteins are becoming better elucidated. The amino acid sequences of many enamel proteins have been identified (Fincham et al, 1983; Ogata et al, 1988), and specific monoclonal antibodies against amelogenins and enamelines have been successfully produced (Christner et al, 1985; Rosenbloom et al, 1986). Furthermore, messenger RNAs for mouse amelogenins have been characterised and these used for the production of cDNA clones by recombinant techniques (Snead et al, 1983; Lau et al, 1987; Snead and Lau, 1987). Thus, important molecular probes are now available to study a number of unresolved problems in amelogenesis.

Recently, investigators have localised the human amelogenin gene to the distal portion of the short arm of the X (p22.1-p22.2) and to the Y chromosome (Lau et al, 1988). These chromosomal locations may explain the molecular pathogenesis for some genetic defects which have been linked to either X or Y chromo-

somal aberrations such as the X-linked forms of amelogenesis imperfecta (Wright & Butler, 1989).

Improved knowledge of enamel proteins and the availability of molecular techniques provide insight into the pathogenetic mechanisms of acquired and inherited types of enamel hypoplasia. Snead and Lau (1987) suggested that enamel defects may be related to perturbation of the (1) genome, (2) transcriptional apparatus or (3) translational machinery. In addition, acquired enamel defects may result from an abnormal composition of enamel matrix proteins caused by displacement of enamel-specific mRNAs by stress-compensating gene products. This response may be analogous to the mammalian "heat-shock" response (Schlesinger, 1986; Pelham, 1986).

Abnormalities in the composition of enamel proteins have been detected in a recent investigation of teeth obtained from a patient with an inherited enamel defect, the hypomaturational-type of amelogenesis imperfecta (Wright & Butler, 1989). The authors reported the presence of excessive amelogenins in the enamel which confirmed a defect in the maturation process of enamel formation.

Enamel matrix composition may also be altered by environmental factors such as chemicals. For example, high levels of fluoride ingestion (greater than 50ppm) have been shown to inhibit the secretion of matrix proteins (Den Besten & Crenshaw,

1987)). In the early-maturation stage of enamel formation, high fluoride levels may lead to retention of amelogenins as a result of inhibition of extracellular proteases responsible for degradation of enamel proteins (Crenshaw & Bawden, 1984). It is likely that abnormal degradation and removal of enamel proteins result in abnormal enamel ultrastructure by interfering with crystallite growth and delineation (Den Besten & Crenshaw, 1984).

Biochemical analysis of abnormal enamel which has resulted from various pathological conditions may thus provide further insight into the complex process of amelogenesis. Also, the clinical diagnosis of many inherited and acquired types of developmental enamel defects may be greatly aided by biochemical analysis of enamel. This possibility may soon become a practical reality with the development of molecular probes for the enamel proteins.

Dentinogenesis

Morphologic events

Dentine is formed by the odontoblasts which differentiate from the ectomesenchymal cells of the dental papilla under the influence of the dental epithelium. Dentine formation begins at the late bell stage of tooth development at the periphery of the papilla (Ten Cate, 1985).

The newly differentiated odontoblast is characterised by a high RNA content, and marked oxidative and hydrolytic enzyme activity. Ultrastructurally, it has a well-developed Golgi complex, numerous mitochondria, many vesicular structures and an extensive microtubular system (Osborn & Ten Cate, 1983). The initial (mantle) dentine matrix deposited against the basal lamina of the internal dental epithelium consists of large fibres formed by the odontoblasts, together with the ground substance. These fibres are generally arranged at right angles to the basement membrane. As the first dentine is formed, the odontoblasts move away towards the centre of the dental papilla and push out odontoblastic processes which eventually occupy tubules in the formed dentine. After deposition of the mantle dentine matrix, the pattern of collagen fibril deposition is changed so that the later-formed circumpulpal dentine contains finer-diameter collagen fibrils arranged in a plane parallel to the basement membrane.

It is now believed that all the collagen of the dentine matrix is produced by the odontoblasts (Ten Cate, 1978; Linde, 1984a). The large, argyrophilic (silver-staining) Von Korff's fibres which were described as originating from the subodontoblastic papillary cells are now considered histological artifacts caused by the capturing of silver by reducing sugars in the ground substance (Ten Cate, 1978).

The mineralization process of mantle dentine appears different to that of circumpulpal dentine. Extracellular matrix vesicles derived from the odontoblasts play an important role in mantle dentine formation (Bonucci, 1984) whereas these vesicles are not observed in circumpulpal dentine mineralization (Linde, 1984a). The apatite crystallites which first appear as single crystals within the matrix grow rapidly and rupture from the confines of the vesicles to spread as clusters of crystallites, until fusion with adjacent clusters to form the fully mineralized matrix (Ten Cate, 1985).

Investigations into the chemistry of matrix vesicles have demonstrated factors within the vesicle suitable for the initiation of mineralization. These include alkaline phosphatase, ATPase and calcium-binding lipids (Bonucci, 1984). It has been suggested that matrix calcification may occur by three possible mechanisms (Ali et al, 1971; Bonucci, 1984): (1) hydrolysis of phosphate esters which induces an increase in the local inorganic phosphate concentration, (2) increase in calcium and phosphate concentration by active transport, with energy supplied by the hydrolysis of ATPase, (3) removal of calcification inhibitors by hydrolysis of pyrophosphates.

In circumpulpal dentine formation, the pulpal aspect of dentine is bordered by an unmineralized collagenous matrix layer known as predentine, which is transformed into dentine after mineralization. The pattern of mineralization in circumpulpal

dentine is calcospheritic, i.e. newly formed mineral spreads radically from growth centres (nuclei) and these coalesce (Shellis, 1983).

In dentine mineralization, organic macromolecules such as the phosphoproteins, glycoproteins and the γ -carboxyglutamate (Gla)-containing proteins are likely to provide the substrates for nucleation of apatite crystals (Jones & Boyde, 1984). These components of the organic matrix of dentine are now believed to have important roles in the control of dentine mineralization. Collagen is thought to provide the fibrous architecture on which apatite crystals are deposited (Linde, 1984a).

The organic matrix of dentine

Collagen

Collagen accounts for approximately 80-90 percent of dentine. The amino acid composition of dentine collagen has been found to be similar to that of skin and other soft tissues except for the presence of two to three times the amount of hydroxylysine (Butler, 1984).

Dentine collagen is now thought to be comprised of mainly Type I collagen with minor amounts of Type I trimer (Sodek & Mandell, 1982). During biosynthesis, Type I trimer appears to be made in relatively large quantities and secreted into predentine (Sodek & Mandell, 1982) but may not be retained since the levels in mature tissue are low (Butler, 1984). Small amounts of Type V

collagen may also be present in dentine. In contrast, Type III collagen which is present in significant quantities in soft tissues and has a likely inhibitory role in mineralization, is not found in normal dentine (Butler, 1984). It has, however, been reported in dentine of patients with osteogenesis imperfecta as well as in patients with dentinogenesis imperfecta (Sauk et al, 1980).

Compared to other collagens, bone and dentine collagens have been found to be highly cross-linked, although the nature and localization of the intermolecular bonds involved have not been completely elucidated. Furthermore, studies have indicated that dentine collagen may be differentiated from bone collagen by the different cross-linking patterns which may relate to different physiological functions (Kuboki & Mechanic, 1982).

The unique features of dentine collagen probably contribute to its function as a matrix for mineralization. However, the exact biochemical mechanisms involved in the deposition of apatite crystals within and around the collagenous fibrillar networks are not completely understood. The results of several studies suggest that the loosely-arranged packing of dentine and bone collagen fibrils is necessary for calcification and that the rigidity of the collagen framework imparted by cross-linking may limit the extent of mineral deposition (Glimcher, 1981). Furthermore, other studies have shown that the formation and deposition of apatite crystals is non-random, indicating the

importance of collagen structure in the process (Glimcher, 1981; Blottner & Wagner, 1989).

Non-collagenous components

Non-collagenous proteins of bone and dentine which constitute 5-10 percent of the total matrix proteins are now thought to play important roles in the calcification process of dentine (Veis, 1988). In the organic matrix, collagen may be considered as the component which defines the system architecture and the non-collagenous proteins as regulating and directing mineral deposition (Veis, 1984).

The non-collagenous proteins are all anionic in character and may be grouped into the following classes: phosphoproteins, γ -carboxyglutamate-containing proteins, acidic glycoproteins, and serum proteins (Linde, 1984a). Different composition of non-collagenous proteins are found in dentine compared to bone. The dentine proteins are rich in aspartic acid and are highly phosphorylated on serine whereas the bone proteins generally have more glutamic acid than aspartic acid (Veis, 1988).

(i) Phosphoproteins

Phosphoproteins constitute the major non-collagenous protein fraction from all mammalian dentine species studied so far (Linde, 1984b). These proteins are rich in serine, phosphorus and aspartic acid and the first major soluble phosphoprotein isolated from bovine dentine was named "phosphophoryn" (DiMuzio &

Veis, 1978). The molecular weights of dentine phosphophoryns differ from species to species: for bovine dentine, a protein of MW 155,000 was obtained, while for the rat, the apparent MW was 90,000 - 95,000 and for mouse the value was 72,000 (Butler, 1987).

Phosphoproteins are thought to play important roles in dentine mineralization for several reasons. Firstly, they are synthesized by odontoblasts and deposited in the mineralization front of dentine (Rahima & Veis, 1988). Using specific monoclonal antibodies directed against bovine phosphophoryn, Nakamura et al (1985) demonstrated that phosphophoryn was present in the odontoblasts, odontoblastic processes and dentine but not in the matrix of predentine, and that the phosphophoryn content of the dentine was high at and around the predentine-dentine junction and gradually decreased towards the enamel layer. Phosphophoryn was not located in mantle dentine. Other investigations using polyclonal antibodies confirmed that the protein is transported through the predentine layer via the odontoblastic processes and secreted distally at the level of the mineralization front (MacDougall et al, 1985; Gorter de Vries & Wisse, 1989).

Secondly, phosphophoryns contain about 40 percent phosphorylated serine residues that possibly donate phosphate for calcium phosphate formation (Takagi & Veis, 1984). The degree of phosphorylation appears to be an important aspect in the functioning of phosphoproteins (Steinfort et al, 1989). Furthermore,

phosphoproteins contain about 40 percent aspartic acid residues and their acidic nature results in high affinity for calcium ions (Stetler-Stevenson & Veis, 1987) as well as induction of calcium precipitation (Kuboki et al, 1979).

Thirdly, phosphophoryns have been shown to accelerate the formation of an apatite-like mineral from solutions of calcium phosphate in-vitro (Nawrot et al, 1976). Furthermore, studies on the interaction of phosphophoryns and collagen suggest that phosphophoryns increase the calcium-binding affinity of collagen fibre surface (Stetler-Stevenson & Veis, 1986). In addition, the conformational change of phosphophoryns induced by calcium may nucleate growth of apatite crystals along the c-axis (Lee & Veis, 1980).

Other studies have also shown that phosphophoryns, once adsorbed to the crystal surface, form a barrier between solution and mineral, and may thus stabilise the pre-existing mineral by inhibiting further mineralization (Termine, 1988).

In addition, recent investigations which showed that enamel-related dentine contains significantly greater amounts of higher phosphorylated phosphoproteins compared to cementum-related dentine indicate that there are differences in the composition of the organic dentine matrix in enamel-related dentine compared with cementum-related dentine (Steinfort et al, 1989). Alterna-

tively, the results may reflect differences in the mineralization process between crown and root dentine (Takagi et al, 1988).

Furthermore, in dentinogenesis imperfecta, the low levels of dentine phosphophoryns in both free and collagen-bound states suggest that there may be a relationship between the absence of these proteins and the abnormal mineralization observed in this condition (Takagi and Sasaki, 1986; Takagi et al, 1983). This finding taken together with the observation that phosphophoryns are not found in mantle, secondary or reparative dentine suggests that dentine phosphophoryns are synthesized and secreted only by physiologically-differentiated odontoblasts but not undifferentiated or degenerated cells (Takagi & Sasaki, 1986).

(ii) Gla-proteins

Gla-proteins are those containing a unique calcium binding site, γ -carboxyglutamic acid (Gla) which is vitamin K-dependent (Price, 1988). Osteocalcin which is a low molecular weight Gla-protein found in bone and dentine is one of the best studied (Termine, 1988).

Gla-proteins have been found in both mantle and circumpulpal dentine, and their constant appearance in various stages of tooth development suggest possible roles in initial as well as continued dentine formation (Gorter de Vries et al, 1987). Dentine Gla-proteins have been shown to be synthesized by odontoblasts and transported in a distal direction via the odontoblast process

(DiMuzio et al, 1983). Most studies have not located Gla-proteins in predentine (Camarda et al, 1987; Bronckers et al, 1987).

Although little is known about the biological role of Gla-proteins in dentine, their apatite-binding properties (Hauschka & Carr, 1982) most likely relate them to specific functions in calcification (Linde, 1984b). In this regard, studies on osteocalcin have provided some clues. The transformation of brushite to hydroxyapatite is inhibited by very low concentrations of osteocalcin and osteocalcin also inhibits the precipitation of hydroxyapatite from supersaturated solutions (Price, 1988). Also, because there are only about 1-2 molecules of osteocalcin for each microcrystal of hydroxyapatite in bone, the binding sites on the microcrystal could have important consequences in mineral crystallization and solubilization kinetics (Hauschka & Carr, 1982). In addition, recent work exploring osteocalcin biosynthesis on stimulation with $1,25(\text{OH})_2$ vitamin D suggests that osteocalcin may be critical to normal bone turnover and metabolism (Termine, 1988).

(iii) Glycoproteins

Glycoproteins are non-collagenous, acidic proteins rich in glutamic acid, aspartic acid and sialic acid (Linde, 1984b). Their importance in bone and dentine formation is indicated by radioautographic studies which showed that they are secreted by osteoblasts and odontoblasts at the mineralization front and may

be involved in controlling the rate and site of mineralization (Weinstock, 1979). Two glycoproteins, bone sialoprotein and osteonectin have been well characterised.

Bone Sialoprotein

A glycoprotein named sialoprotein because of its high content of sialic acid, was one of the first bone proteins to be identified. It is now known that the 23,000 dalton species originally described is a proteolytic degradation product of a 80,000 dalton parent molecule (Termine, 1988). Bone contains two sialoproteins that account for 5-6 percent of the non-collagen protein (Fisher et al, 1987). One of these, with a lower sialic acid content, was initially called bone sialoprotein I, but was later renamed osteopontin when analysis of the primary sequence of this protein revealed that it contained an internal fibronectin-like, cell-attachment sequence (Oldberg et al, 1986). Osteopontin may serve as an attachment protein for gingival fibroblasts in-vitro (Termine, 1988).

The major human and bovine sialoprotein is called bone sialoprotein II (Fisher et al, 1987). Complementary-DNAs encoding human bone sialoprotein II have now been obtained (Termine, 1988).

Osteonectin

Osteonectin is an abundant non-collagen protein found in bone. However, the amount of osteonectin in dentine appears to

vary greatly among different animal species (Zung et al, 1986). Studies on fetal (Termine et al, 1981) as well as adult (Romberg et al, 1985) bovine bone show that osteonectin binds both calcium ions and hydroxyapatite strongly. It also binds tightly to native collagen (Romberg et al, 1985). Although in solution osteonectin is a potent inhibitor of hydroxyapatite crystal growth and replication (Romberg et al, 1985), in the bound state, it promotes calcium phosphate deposition from metastable solutions (Termine et al, 1981). Although the functions of osteonectin are still unclear, it is likely to play a vital role in the extracellular calcification process.

Root formation and cementogenesis

In the bell stage of dental development, the cervical loop grows to form a double layer of epithelial cells known as Hertwig's root sheath which grows basally between the tooth follicle and dental papilla (Ten Cate, 1985). During development, Hertwig's root sheath encloses the papilla except for the primary apical foramen. In a molar tooth, the papilla develops into lobes and bays which correspond in number and location with the definitive roots (Osborn & Ten Cate, 1983). Secondary apical foramina which are found at the root apices are formed by the inward growth of the epithelial tissue. Local defects may occur at tissue junctions producing pulpo-periodontal canals commonly

found in the root furcation regions of deciduous molars (Ten Cate, 1985).

As Hertwig's sheath grows vertically, it induces the differentiation of odontoblasts at the papilla surface (Thomas & Kollar, 1989). The odontoblasts produce the dentine of the root which lengthens in an apical direction.

The importance of Hertwig's root sheath in root formation is becoming increasingly recognised. Besides the induction of odontoblast formation, it initiates the differentiation of cementoblasts from ectomesenchymal cells of the follicle (Owens, 1980; Lindskog, 1982; Slavkin, 1979). Furthermore, the cells of Hertwig's sheath are now known to produce a layer of first-formed cementum termed "intermediate cementum" which is formed prior to the uncoupling of the root sheath (Lindskog, 1982; Owens, 1978).

Recent studies have indicated that proteins isolated from intermediate cementum may provide the instruction for ectomesenchyme differentiation to become cementoblasts (Slavkin et al, 1988b; 1989). Although these intermediate cementum proteins have been found to share one or more epitopes with enamelin and amelogenin enamel proteins, they have different amino-acid compositions and are considered unique cementum proteins (Slavkin et al, 1989). While the role of these intermediate cementum proteins is not completely known at present, they are likely to be involved in the regulation of root formation by Hertwig's

sheath. In this regard, recent work by Thomas and Kollar (1989) has shown that recombinations between Hertwig's root sheath and fetal dental papilla ectomesenchyme may result in either dentine or bone formation depending on the age of the ectomesenchymal tissue.

Chronology of development of the primary dentition

Accurate knowledge of the chronology of development of the teeth is of significance in the diagnosis of various systemic and local disturbances which affect tooth formation. Since the mid-nineteenth century, several investigations have attempted to determine initial calcification times of the primary teeth by examination of jaws of human fetuses and young infants (Lunt and Law, 1974). Kraus and Jordan (1965) provided one of the largest series of over 700 fetuses. According to these authors, the primary tooth germs have undergone histodifferentiation and begun morphodifferentiation during the first six weeks of intrauterine life. The second primary molar germs appear at about the seventh week. However, calcification of the primary central incisor does not start until fourteen weeks; for the lateral incisor at sixteen weeks, for the canine at seventeen weeks, the first molar at fifteen and a half weeks; and for the second molar at nineteen weeks.

As the rate of apposition of hard tissue is considered to be approximately 4 μ m per 24 hours (Schour and Massler, 1940), enamel formation is incomplete for all the primary teeth at the end of a normal pregnancy lasting approximately forty weeks. As a result of extensive comparative studies of previous literature, Lunt and Law (1974) suggested several changes to the original calcification times originally proposed by Logan and Kronfeld in 1933. According to Lunt and Law, the amount of enamel formed at birth for the maxillary primary central incisor is $5/6$, lateral incisor $2/3$, canine $1/3$, first molar occlusal surface plus $1/2 - 3/4$ crown height, and the second molar occlusal surface plus $1/5 - 1/4$ crown height. The amount of enamel formed for the mandibular primary teeth are: central incisor $3/5$, lateral incisor $3/5$, canine $1/3$, first molar occlusal surface and second molar occlusal surfaces incompletely mineralized.

However, infants born preterm will have less enamel formed at birth, the actual amount present varying with gestational age.

Developmental Defects of Enamel

Developmental enamel defects may result from both inherited and acquired aetiological factors. The defects associated with systemic disturbances are usually generalised, affecting several groups of teeth which were undergoing amelogenesis at the time of disturbance. In contrast, the defects arising from local aetiological factors usually affect single teeth or localised groups of teeth.

Inherited types of enamel defects

Inherited defects of enamel may be broadly classified into two general types (Table 1.1). The first type occurs unassociated with evidence of systemic disease and is collectively known under the title of amelogenesis imperfecta. Since the term was coined in 1945 by Weinmann et al, several varieties of the condition have been reported, each with a different mode of genetic transmission as well as distinct clinical features. The prevalence of all types of amelogenesis imperfecta in the general population is about 1 in 14,000 (Winter and Brook, 1975).

The second type of inherited enamel defect occurs in association with a number of generalised systemic syndromes. Many of these result from a defect of ectodermal origin e.g. ectodermal dysplasia and epidermolysis bullosa, or a defect of both ectodermal and mesodermal tissues e.g. tricho-dento-osseous syndrome. Others

May be associated with inherited metabolic disease e.g. porphyria and hypoparathyroidism or dysmorphic syndromes of unknown origin e.g. Nance-Horan syndrome (Seow et al, 1985a); *hereditary microsomia* (Robertson et al, 1990)

Acquired types of enamel defects

Of all the organ systems in the body, the teeth have the most prolonged period of development (Stewart et al, 1982). In addition, the lack of remodelling of the enamel surface after completion of mineralization provides a permanent record of any disturbance occurring during amelogenesis. Acquired causes of developmental

Table 1.1 Classification of Inherited Types of Enamel Defects

I. Inherited defects of enamel

- Amelogenesis Imperfecta i) Hypoplastic
 ii) Hypocalcified
 iii) Hypomature

II. Inherited systemic conditions with enamel defect

1. Related to ectodermal dysplasias
2. Related to inherited disorders of calcium metabolism
 - i) hypoparathyroidism and related diseases
 - ii) vitamin D-dependency rickets
3. Other syndromes
 - i) tricho-dento-osseous
 - ii) epidermolysis bullosa
 - iii) oculodentodigital dysplasia
 - iv) mucopolysaccharidoses
 - v) hemifacial microsomia

enamel defects may be both systemic and local, and these may occur prenatally, perinatally or postnatally.

Systemic defects

Table 1.2 lists various systemic factors which have been previously associated with enamel hypoplasia. As can be seen from the table, the factors are diverse and may be classified as birth trauma, infections, nutritional disorders, metabolic disorders and chemical intoxication. However, although the relationship between these causative factors and enamel hypoplasia have been well described, the actual mechanisms of tissue damage are not well understood. In addition, there are other conditions associated with enamel hypoplasia for which causal relationships are not established.

(i) Birth trauma

Even the normal birth process may be recorded as a line of enamel hypoplasia known as the neonatal line which is observed in microscopic sections (Rushton, 1933). The changes in enamel are thought to result from the trauma of transition from intra-uterine to extra-uterine life (Kronfeld and Schour, 1939). Several adverse factors occurring during the neonatal period may accentuate the neonatal line, making it macroscopically evident (Stewart et al, 1982).

Table 1.2 Systemic Factors Associated with Enamel Hypoplasia

	Prenatal	Perinatal	Postnatal
Birth Trauma		Breech presentation, multiple pregnancy, Caesarian section, prolonged labour	
Infections	Maternal infections, e.g. Syphilis, Rubella, Measles, Chicken Pox	Congenital Syphilis, Congenital Rubella, Congenital Cytomegalovirus	Measles, Chicken Pox, Scarlet Fever, Pneumonia, Gastro-intestinal infections
Nutritional disorders	Maternal Vitamin D deficiency	Vitamin D deficiency	Vitamin A or D deficiency
Metabolic Diseases	Maternal hypoxia, Toxaemia of pregnancy, maternal diabetes	Hyperbilirubinaemia, Neonatal asphyxia, Hypocalcaemia, prematurity complications	Hypothyroidism, Hypoparathyroidism, Congenital cardiac diseases, Gastrointestinal malabsorption, Nephrotic syndrome, Chronic renal failure, Biliary atresia
Chemicals	Tetracycline, Thalidomide	Tetracycline	Tetracycline, Lead intoxication, excessive fluoride

Difficult birth such as breech presentation, prolonged labour, multiple pregnancy and caesarian section have been associated with enamel hypoplasia (Via and Churchill, 1959; Funakoshi et al, 1981). In these conditions, the enamel defects probably result from metabolic changes resulting from fetal stress.

(ii) Infections

Severe infections occurring during amelogenesis may be associated with enamel hypoplasia. The mechanisms of damage may be related to direct cellular damage by the infecting microorganisms, although secondary systemic insults may arise from malfunctions of the major organs affected. Furthermore, the increase in body temperature observed in many infections may also cause ameloblastic derangements (Kreshover and Clough, 1953).

Congenital infections with syphilis and rubella have been well documented to result in enamel hypoplasia of both primary and permanent dentitions (Fiumara and Lessell, 1969; Brauer and Blackstone, 1941; De Wilde, 1943; Guggenheimer et al, 1971; Musselman, 1968). In addition, a recent study has shown that congenital cytomegalovirus infection is also associated with a high prevalence of enamel defects of the primary dentition (Stagno et al, 1982).

Post natal infections with exanthematous diseases such as measles, chicken pox and scarlet fever as well as severe respiratory infections have all been associated with enamel hypoplasia

(Kreshover, 1960; Giro, 1947; Sarnat and Schour, 1942; Sparber, 1967). In addition, severe gastroenteritis has also been reported to result in enamel defects (Smith and Miller, 1979; Infante and Gillespie, 1977; Woodward et al, 1974) although it is unclear whether the cause is directly related to the infection or is secondary to the resulting malabsorption.

It is of interest to note, however, that many children with a history of severe febrile infections do not show developmental dental defects, indicating that the relationship is not a simple one.

(iii) Nutritional disorders

In some under-developed countries, a specific developmental defect of primary teeth called linear enamel hypoplasia is commonly encountered. For example, its prevalence in Guatemala and in San Blas Islands off the Panama coast, has been reported to be around 42 and 31 percent respectively (Sweeney et al, 1971; Jelliffe et al, 1961). The aetiology of this type of enamel hypoplasia is not fully understood, but it is likely to result from the synergistic action of malnutrition and infection (Sweeney et al, 1971; Scrimshaw et al, 1968).

Although it is reasonable to assume that ameloblasts are affected by severe general malnutrition, deficiency of certain nutritional elements directly associated with epithelial cell function and the mineralization process must be particularly important. These include the vitamins A and D; deficiencies of these

vitamins have been documented to result in enamel hypoplasia (Mellanby, 1941; Punyasingh et al, 1984; Hurmerinta et al, 1980; Purvis et al, 1973; Berdal et al, 1987).

(iv) Metabolic diseases

Several metabolic disturbances which occur prenatally, perinatally and postnatally affect enamel development.

(a) Maternal diabetes and hypertension: These conditions are associated with an increased prevalence of enamel hypoplasia in the primary dentition (Grahnen and Edlund, 1967; Kreshover et al, 1958; Via and Churchill, 1959). However, it is unclear as to whether the cause is directly related to these diseases or to some secondary disturbance associated with these conditions such as hypocalcaemia.

(b) Hyperbilirubinaemia: Hypoplastic teeth stained green had been associated with jaundice and haemolytic disease of the newborn since 1912 by Thursfield. Before the availability of effective control measures for haemolytic diseases of the newborn, enamel hypoplasia and intrinsic green staining of the teeth by bilirubin pigment were common observations in affected children (Losch et al, 1940; Tank 1951; Forrester and Miller, 1955). In addition, Miller (1951) demonstrated that the green pigment was located in a band in dentine at the level of neonatal development.

Was it
not
associated
prior to
1912?

Although seldom seen in recent times, a recent case report described green pigmentation and enamel hypoplasia in a prematurely-born child who suffered hyperbilirubinaemia in the neonatal period (Herbert and Delcambre, 1987).

- (c) Hypocalcaemia: As calcium metabolism is directly involved in dental development, it is not surprising that in conditions which demonstrated disturbed calcium metabolism, enamel hypoplasia is often noted. As early as 1941, Gaunt and Irving demonstrated in animal experiments that hypocalcaemia caused severe disturbances of tooth calcification. Later, a clinical study by Grahnen and Selander (1954) reported that there was a significant increase in the frequency of enamel hypoplasia in a group of children who suffered hypocalcaemic tetany (73 percent) compared with a control group of normal healthy children (3 percent). In addition, Stimmler et al (1973) showed that all patients in their study who had neonatal hypocalcaemia resulting from the feeding of unfortified cow's milk had enamel hypoplasia which was severe in spite of the short duration of hypocalcaemia. A microscopic study of such hypoplastic teeth confirmed that the enamel defect occurred during the neonatal period (Levin and Keen, 1974).

Further confirmation of the association of derangements of calcium metabolism and enamel hypoplasia is provided by the study of Seow et al (1984b) which investigated a group of prematurely-born children who suffered neonatal rickets. In this report, all the 15 affected children showed enamel

hypoplasia. In addition, hypocalcaemia resulting from abnormalities of the parathyroid glands have also been associated with severe enamel hypoplasia (Albright and Stock, 1933; Ritchie, 1965; Pisanty and Garfunkel, 1977; Nikiforuk and Fraser, 1979).

- (d) Other metabolic diseases: Metabolic diseases associated with many other organ systems have also been implicated in enamel hypoplasia. These include congenital cardiac diseases (Bouyssou, 1962; Berger, 1978) and renal diseases such as nephrotic syndrome (Shusterman and Fellers, 1969) and chronic renal failure (Woodhead et al, 1982). As well, liver diseases such as biliary atresia have also been associated with severe enamel defects (Belanger et al, 1982).

(v) Chemicals

(a) Tetracyclines

Enamel hypoplasia and tooth discolouration caused by tetracyclines became widely appreciated in the early 1960's (Owen, 1963). Tetracyclines given after the eighth week of pregnancy may pass through the placenta to affect the developing fetal dentition. Direct toxicity to the ameloblasts and disruption of the mineralization process are possible mechanisms of damage (Nylen et al, 1972; Baker, 1972).

(b) Fluoride

The effects of excessive fluoride in causing enamel hypoplasia have now been well documented since Dean (1936) showed unequivocally that the prevalence and severity of dental fluorosis is determined by the fluoride concentration in the drinking water (Nanda et al, 1974; Pu and Lilienthal, 1961; Leatherwood et al, 1965; Minoguchi, 1970; Forsmann, 1977). However, the mechanisms whereby fluoride produces enamel changes are still unclear (for review see Fejerskov et al, 1977, 1983).

It is generally accepted that dental fluorosis is more obvious in the permanent dentition (Babeaux and Zipkin, 1966), although severe fluorosis may be observed in the primary dentition where the fluoride content exceeded six parts per million or six times optimal in temperate climates (Smith and Smith, 1935; Forsmann, 1974).

Local factors

Since Turner (1912) first described a localised type of enamel hypoplasia resulting from infection of primary teeth, many clinical reports have confirmed that local factors are important causes of tooth defects (Andreasen and Ravn, 1973; Pindborg, 1970; Ideberg and Persson, 1971; Ravn, 1976; Seow et al, 1984a).

(i) Trauma to developing teeth

Trauma to developing teeth may result in derangement of tooth development ranging from minimal lesions such as an enamel opacity to severe changes manifested as enamel hypoplasia or even crown

and/or root dilaceration. Animal studies have provided direct evidence of these effects of trauma (Andreasen, 1976; Suckling, 1980). Clinically, the most well-known types of defects are those observed on permanent teeth following trauma to their primary predecessors. According to Andreasen and Ravn (1973), as much as 10 percent of enamel hypoplasias affecting permanent anterior teeth in school children in Copenhagen were due to trauma to the primary dentition. Other studies showed that the type of trauma sustained determines the degree of developmental disturbance, with avulsion and intrusive luxation representing injuries with very high frequencies of developmental disturbances compared with subluxation and extrusion (Andreasen and Ravn, 1973; Ravn 1975; 1976). Furthermore, the age at the time of injury is of major importance, with fewer complications seen in individuals above 4 years of age than in younger individuals (Andreasen and Ravn, 1973).

Other forms of trauma to developing teeth which have been previously documented include jaw fractures (Ideberg and Persson, 1971; Lenstrup, 1955; Ridell and Astrand, 1971), surgical trauma (Dixon, 1968; Mink, 1959), gunshot injuries (Pindborg, 1970) and electrical burns (Alexander, 1964).

(ii) Local infections

Periapical infections of primary teeth causing enamel hypoplasia of succedaneous permanent teeth are also well known (Turner, 1912; McCormack and Filostrat, 1967). Acute local

osteomyelitis has also been established as a cause of enamel hypoplasia (Pindborg, 1970).

(iii) Other local causes of enamel hypoplasia

Irradiation has been known to cause enamel hypoplasia (Weyman, 1968) although ameloblasts have been reported to be generally resistant to low levels of irradiation (McDonald and Avery, 1978).

Ankylosis of primary teeth has also been associated with an increased frequency of enamel hypoplasia in the succeeding permanent teeth (Weiss, 1963; Rule 1972), although the reason for this association is unknown.

Dental Defects in Prematurely-born Children

As early as 1936, Stein reported that five out of twelve prematurely-born children examined had enamel hypoplasia in the deciduous dentition. These children were found to have higher caries prevalence and an increased tendency to tooth discolouration. Two years later, Schour and Kronfeld (1938) reported enamel hypoplasia in a child born prematurely. The authors associated the hypoplasia with brain injury at birth.

In another study on 16 children, born mostly in the seventh month of pregnancy, Stein (1947) found that eight had macroscopic hypoplasia located in the incisal third of the tooth. He stated that "several hundreds" of full-term children were examined as a control

group and, amongst these, found only one with enamel hypoplasia in the deciduous dentition. Histological examination of the hypoplastic teeth revealed that the striae of Retzius were accentuated as continuations of the enamel hypoplasia. In this investigation, however, Stein did not describe his method of selecting his subjects, and therefore it is difficult to assess the true frequency of enamel defects in his study population.

Forrester and Miller (1955) found that of 34 prematurely-born children, seven (20 percent) had severe enamel hypoplasia in the deciduous dentition. The frequency is much higher in the study of Kreshover et al (1958) in which a selected series of 35 children, varying in age from premature stillborns to infants up to two and a half months were examined. Histological examinations revealed that developmental enamel defects were present in 77 percent of the premature babies.

In a study of 68 prematurely-born children with birth weights $\leq 2500\text{g}$ and a control group of 61 full-term children with birth weight $\geq 3000\text{g}$, Grahnen and Larsson (1958) found that enamel hypoplasia was present in 21 percent of the prematurely-born group compared with only 2 percent of the control group. These results clearly show that prematurity was significantly associated with enamel hypoplasia.

Rosenzweig and Sahar (1962) examined 21 prematurely-born Jewish infants and reported that enamel hypoplasia was present in eight of them (23.8 percent). In the matched, control group of 80

children, only one child had questionable enamel hypoplasia.

In a later study on premature infants, Grahnen et al (1974) reported that 22 percent of them had enamel hypoplasia compared with 5 percent of controls. In addition, 21 percent had enamel opacities compared with 10 percent of controls. On analysis of the medical problems suffered by the premature infants, Grahnen concluded that prematurity per se is not a cause of enamel hypoplasia, rather it is the complications of prematurity that appear to be causative. In contrast to his earlier work (Grahnen et al., 1969), Grahnen suggested that birth asphyxia is an important cause of enamel hypoplasia in his study group.

In a study by Funakoshi et al (1981), an attempt was made to identify certain factors associated with enamel hypoplasia in a group of premature infants with mean birth weight of 1612g. The authors reported that there was no significant difference in the frequency of enamel hypoplasia in the infants whose birth weights were small for gestational age. However, the frequency was much higher for those less than 34 weeks gestation and in those infants who weighed <2100g at birth. The overall frequency of enamel hypoplasia was 26.9 percent. Although the authors listed several neonatal complications commonly present in premature infants, it was unclear from the study whether any of these had a definite role in the aetiology of enamel hypoplasia.

The study by Mellander et al (1982) on 91 premature infants with low birth weight showed that 32 percent of such children had

enamel hypoplasia and opacities. The only significant aetiological factor that the authors could relate to the hypoplasia was a lower intake of unsupplemented breast milk during the first week of life. Another factor considered was idiopathic respiratory distress syndrome; however, infants with this condition also had significantly lower breast milk intake.

In the more recent investigation by Johnsen et al (1984) on 67 very low birth-weight children (<1500 g), a prevalence of enamel hypoplasia of 21 percent was found. In addition, enamel opacities were observed in an additional 31 percent, giving a total prevalence of enamel defects of 52 percent. In this study, a few medical risk factors were considered as possible aetiological causes but the only condition reported to be of significance was respiratory distress.

In 1985 Pimlott et al reported that 38 percent of 106 very low birthweight children had defective primary maxillary incisors. Of even greater significance was their finding that enamel opacities were observed in maxillary permanent incisors in 58 percent of the sample. As in the study of Johnsen et al (1984), no correlation could be demonstrated between enamel defects and many birth parameters such as plasma calcium levels.

Fearn, Bryan and Brook (1990) report 71% of low birth weight infants had enamel hypoplasia.

It is thus apparent from previous literature that the prevalence of enamel hypoplasia in premature infants is significantly higher than those born full-term. With increasing sophistication of neonatal care in recent years, there is greater survival of infants born with extremely low birth weights. However,

with the exception of a few recent studies, very few infants of birthweight <1500 g were included in the investigations.

Review of previous literature also indicates that while it is well recognised that the prematurely-born infant has serious systemic complications, none of these could be definitely identified as being more significant over the others in the pathogenesis of enamel defects.

Developmental Defects of Dentine

Developmental defects of dentine may arise from acquired and inherited causes. Acquired causes of dentine defects are similar to those associated with developmental enamel defects (Table 1.2), and many acquired systemic illnesses which may cause enamel hypoplasia may also result in dentine malformations. However, distinct dentine anomalies may be noted in many inherited types of diseases. These genetic conditions may be classified into 2 broad groups, one showing dentine abnormalities only and the other showing dentine changes with systemic involvement (Table 1.3).

Inherited defects of dentine

One of the most well known inherited defects of dentine is dentinogenesis imperfecta. Although this condition may be seen in some types of osteogenesis imperfecta (Levin, 1981; Gage, 1985), the prototype of dentinogenesis imperfecta does not have systemic involvement, and shows a prevalence of about 1:8000 (Witkop, 1975).

Table 1.3 Classification of Inherited Types of of Dentine Defects

I.	<u>Inherited defects of dentine</u>
	i) Dentinogenesis imperfecta
	ii) Dentinal dysplasia
	iii) Radicular dysplasia
II.	<u>Inherited systemic conditions with dentine defect</u>
1.	Rickets related
	i) Vitamin D-resistant rickets
	ii) Hypophosphatasia
2.	Other syndromes
	i) Osteogenesis imperfecta
	ii) Tricho-dento-osseous
	iii) Calcinosiis
	iv) Brachio-skeletal-genital syndrome

The classical features of this condition are an autosomal dominant inheritance, brownish-blue discolouration of the teeth, bulbous crowns, short roots, obliteration of the pulp, as well as premature wear of the dentition (Walter, 1988).

Other types of inherited dentine defects have been classified as coronal dentine dysplasia, radicular dysplasia and pulp dysplasia (Witkop, 1975). Coronal dentine dysplasia which has also been classified as dentine dysplasia type II by Shields et al (1973), shows clinical features of amber, translucent discolouration of the primary dentition as well as coronal pulp obliteration and normal roots in both primary and permanent dentitions (Witkop, 1975).

In contrast, radicular dentine dysplasia or dentine dysplasia type I (Shields et al, 1973) shows characteristic features of blunted, abnormal roots with calcified, radicular pulp and coronal pulp chambers typically in the demilune form (Witkop, 1975).

Inherited systemic conditions with dentine involvement

Many types of inherited disease which manifest as rickets also show developmental defects of dentine. These include vitamin D-resistant rickets, as well hypophosphatasia, which is a deficiency of alkaline phosphatase activity caused by an abnormality of enzyme structure (Witkop, 1975).

Dentine defects also accompany many multiple-system malformation syndromes. These include many forms of osteogenesis

imperfecta which show features of dentinogenesis imperfecta (Levin, 1981; Gage 1985). In the tricho-dento-osseous syndrome, hypocalcification of dentine is observed (Jorgenson and Warson, 1973) and in calcinosis, short roots and excessive pulp calcification are constant features (Hunter et al, 1973). Also, in the lesser known brachio-skeleto-genital syndrome, abnormal dentine closely resembling that seen in radicular dentine dysplasia is often found (Witkop, 1975).

Vitamin D-Resistant Rickets

Introduction

Rickets may be defined as failure to mineralise growing bone or osteoid tissue (Barnes, 1987). The term is usually applied to children, the equivalent term osteomalacia being given to adults. Although rickets had been traditionally linked with vitamin D deficiency, it is well known that there are many types of rickets which do not respond satisfactorily to vitamin D supplementation alone. These forms of rickets, known as vitamin D-refractory rickets arise from defects other than those involved in vitamin D metabolism. They include deficiencies in supply or transport of calcium and phosphorus as well as inherited matrix defects of bone. Table 1.4 lists the possible causes of rickets which are resistant to vitamin D.

Of all the conditions listed in Table 1.4, familial hypophosphataemia is the most common; hence the term "vitamin D-

Table 1.4 Causes of rickets refractory to Vitamin D

Cause	Low calcium	Low phosphorus	Matrix defect
Dietary	Calcium deprivation	Phosphate deprivation	
Transport	Malabsorption	1. X-linked hypophosphataemia	
	(a) ↓ vitamin D absorption in bile salts depletion	2. Fanconi's syndrome	
	(b) ↓ calcium, vitamin D absorption in sprue, coeliac disease		
Metabolic	1. Hepatocellular disease with defective synthesis of 25 hydroxy-vitamin D		1. Hypophosphatasia
	2. Long term anticonvulsant use		2. Metaphyseal dysostosis
	3. Renal cortical diseases with defective synthesis of 1,25 dihydroxy-vitamin D		
	4. Autosomal recessive vitamin D-dependent rickets		

resistant rickets" (VDRR) is often used synonymously with the condition. Other names include vitamin D-refractory rickets (Gigliotti et al, 1971), hereditary hypophosphataemia (Gardner et al, 1969) and X-linked hypophosphataemia (Fraser and Sriver, 1976; Seow, 1984a).

Mode of inheritance

The usual mode of inheritance is X-linked dominant (Fraser and Sriver, 1976), although autosomal recessive (Dent et al, 1968) and autosomal dominant types (McKusick, 1978) as well as sporadic cases have also been reported.

Pathogenesis

Although the precise aetiology of the disease is unknown, the well established defect in VDRR is a selective disorder of transepithelial transport of orthophosphate in the proximal tubules of the kidney (Fraser and Sriver, 1976). This leads to decreased reabsorption of phosphate, even at the extremely low levels of serum phosphate found in the disease (Glorieux and Sriver, 1972). The renal loss of phosphate may be further exacerbated by a similar defect of phosphate transport in the intestine (Short et al, 1973).

In addition, a defect in vitamin D metabolism may exist as shown by the impairment of conversion of $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$ (Avioli et al, 1967). This is proven by low serum $1,25(\text{OH})_2\text{D}$ levels despite the hypophosphataemia and the observation that further

phosphate depletion in VDRR patients does not stimulate $1,25\text{ (OH)}_2\text{D}$ synthesis as it does in healthy controls (Glorieux et al, 1980).

It is also likely that a metabolic bone defect exists in the pathogenesis of VDRR (Ecarot-Charrier and Glorieux, 1983). This is shown by the fact that phosphate supplementation with or without pharmacologic amounts of vitamin D heals the rachitic lesions but not the mineralization defect at the trabecular bone surface (Glorieux et al, 1980).

General medical manifestations

Infants with VDRR usually appear healthy and show few clinical manifestations of the disease until about 8-10 months of age (Norman, 1987). This is probably due to the low glomerular filtration rate of infancy inhibiting the loss of phosphate in the urine and this prevents hypophosphataemia (Harrison and Harrison, 1964).

An early clinical sign in affected children is bowing of the lower extremities related to weight-bearing at the age of walking. Other signs of rickets characteristic in the calcium-deficient types such as tetany, myopathy, rachitic rosary and pectus deformity are usually absent (Norman, 1987). The rachitic deformities usually result in disproportionate dwarfism. In addition, retarded skeletal maturation unrelated to growth hormone has also been reported (Archard and Witkop, 1966; Tracy and Campbell, 1968). Harrison et al (1966) also suggested from clinical observations that growth

retardation may be associated with phosphate deficiency alone.

Radiographic findings include metaphyseal widening and fraying and coarse-appearing trabecular bone. At the proximal and distal ends of the tibia and at the distal ends of the femur, radius and ulna, cupping of the metaphysis may occur (Norman, 1987).

Laboratory findings usually consist of a normal or slightly reduced serum calcium level (9.0-9.4 mg/dL), a moderately reduced serum phosphate level (1.5-3.0 mg/dL), elevated alkaline phosphatase activity but no evidence of secondary hyperparathyroidism (Scriver 1974). In addition, urinary excretion of phosphate is large. Characteristically, there is no aminoaciduria, glucosuria, bicarbonaturia and kaliuria (Norman, 1987).

Medical treatment

The usual management regimen is oral phosphate supplements coupled with a vitamin D analogue to prevent development of secondary hyperparathyroidism which may accompany an oral phosphate load (Scriver et al, 1981). Young children should receive phosphate at the dose of 0.5-1.0 g/24 hr. while older children require 1.0-4.0 g daily. Previously, vitamin D₂ was used at 2000 IU/kg/24 hr but more recently, dihydrotachysterol at a dose of 0.02 mg/kg/24 hr or 1,25(OH)₂D at 20-50 mg/kg/24 hr has been used (Lyles and Drezner, 1982).

Dental Manifestations

Although the general signs and symptoms of VDRR had been recognised since the 1930's it was not until 1960 that Harris and Sullivan documented for the first time, the dental signs characteristic of the disease. Various case reports, summarised in Table 1.5 have since confirmed and extended the observations of Harris and Sullivan. The fact that many cases of VDRR were first diagnosed by dentists points out the importance of dental signs in this disease, as general signs and symptoms may be minimal and easily missed.

(i) General dental presentation

The most well known symptoms are multiple abscesses, fistulae and fractured teeth which are not associated with decay or trauma (Archard and Witkop, 1966; Tracy and Campbell, 1968; Harris and Sullivan, 1960; Seow, 1984a; Vasilakis et al, 1980; Tulloch and Andrews 1983; Yasufuku et al, 1983). However, analysis of reported cases in the literature (Table 1.5) indicates that the dental manifestations are variable among VDRR-affected patients.

(ii) Radiographic features

Radiographic examination usually shows the pulp chambers to be unusually large (Table 1.5). However this is based on subjective analysis by the authors as normal standards for pulp chamber sizes for different ages are not available. Other radiographic features

TABLE 1.5
Summary of dental findings in familial hypophosphataemic vitamin D-resistant rickets

Authors	Year	No. of cases	Dentition affected	Dental findings						
				Abcessed teeth chambers	Enlarged pulp	Globular dentine	Abnormal alveolar bone	Delayed eruption	Enamel defects	
Harris and Sullivan	1960	1	Primary	P	P	P	-	-	-	
Marks, Lindehl & Bowden	1965	9	Primary & permanent	2/9	3/9	4/9	4/9	1/9	1/9	
Archard & Witkop	1966	1	Primary	P	P	P	-	-	A	
Soni & Marks	1967	5	Primary & permanent	-	-	5/5	-	-	1/6	
Via	1967	1	Primary & permanent	P	P	P	P	P	P	
Tracy & Campbell	1968	9	Primary & permanent	3/9	3/9	-	-	A	-	
Gardner & Prescott	1969	2	Primary & permanent	2/2	2/2	-	-	-	-	
Wihr	1970	1	Primary	P	P	-	-	-	P	
Tracy et al	1971	7	-	-	-	6/7	-	-	-	
Gigliotti et al	1971	3	Permanent	-	2/3	-	-	-	-	
Sauk & Witkop	1973	1	Primary	-	P	P	-	-	A	
Pliskin et al	1975	1	Permanent	P	P	P	-	P	-	
Cohen & Becker	1976	1	Primary & permanent	P	P	-	-	-	-	
Callo & Merle	1979	1	Primary	P	P	-	A	-	P	
Vasilakis et al	1980	1	Permanent	P	P	P	-	-	A	
Tulloch & Andrews	1983	3	Primary & permanent	3/3	2/3	3/3	1/3	-	1/3	
Yasufuku et al	1983	1	Primary	P	P	P	-	-	A	
Seow	1984	1	Primary	P	P	P	P	-	A	
Breen	1986	1	Primary	P	P	P	-	-	A	
Herbert	1986	1	Primary	P	P	-	-	-	A	

- denotes feature not mentioned by authors

P noted as present by authors

A noted as absent by authors

include the projection of pulp horns close to the dentinoenamel junction and the presence of clefts and deficiencies within the dentine. In addition, periapical radiolucencies resulting from long-standing infections are usually obvious. Abnormalities of the alveolar bone, such as indistinct lamina dura, thinning of cortical plate and lacy trabeculation have also been reported as subjective observations (Tracy and Campbell, 1968; Marks et al, 1965; Gallo and Merle, 1979).

(iii) Enamel defects

Although enamel hypoplasia has been reported (Marks et al, 1965; Via, 1967; Vasilakis et al, 1980; Soni and Marks, 1967; Gallo and Merle, 1979; Tulloch and Andrews, 1983), it does not appear to be a consistent finding. Histological studies however, have not revealed any ultrastructural changes in enamel in those teeth which did not show clinically-evident enamel hypoplasia (Tracy et al, 1971).

(iv) Dentine defects

Defects in dentine are characteristic features of VDRR. Typically, the dentine is thin, and consists of large calcospherites or globules of abnormally-mineralized dentine, often known as interglobular dentine, although the term "globular" dentine is probably more accurate. In addition, dentinal clefts or voids in the dentine occur in the region of the pulp horns (Archard and Witkop, 1966; Tracy and Campbell, 1968). These defects usually

extend to the dentinoenamel junction and allow direct invasion of microorganisms into the pulp once enamel is removed either through abrasion, minimal decay or restorative procedures.

In addition, an absence of secondary dentine formation in VDRR-affected teeth has been reported (Via, 1967; Soni and Marks, 1967), and the loss of this protective mechanism may contribute to the early invasion of the pulp by oral microorganisms. However, lack of secondary dentine formation may also be due to early pulp necrosis.

Radicular dentine and cementum in VDRR have also been studied. Soni and Marks (1967) reported that although cementum formation appeared normal, globular dentine was also present in the root, with an accentuation of Tomes' granular layer.

(v) Other dental findings

Delayed dental eruption has been reported in some patients with VDRR (Marks et al, 1965; Via, 1967; Vasilakis et al, 1980; Soni and Marks, 1967; Gallo and Merle, 1979) but other investigators have refuted this (Archard and Witkop, 1966; Sauk and Witkop, 1973). While it is possible that delayed dental eruption is a feature of VDRR, it is also likely that very early extraction of abscessed primary teeth leads to delayed eruption of permanent successors (Fanning, 1961).

Abnormalities of Tooth Number and Morphology

Abnormalities of tooth number

Alteration in the number of teeth may be expressed as agenesis of teeth or supernumerary teeth. Like other dental anomalies, these conditions may be observed as isolated dental aberrations or they may accompany various systemic syndromes as dysmorphic features.

Agenesis of teeth

A few terms have been commonly used to describe agenesis of teeth. Hypodontia is usually used to mean the absence of one or a few teeth (Stewart et al, 1982) whereas the term oligodontia is often applied for agenesis of numerous teeth, especially when associated with specific syndromes and/or severe systemic abnormalities (Stewart et al 1982; Gorlin et al 1978). Anodontia which indicates total absence of teeth, has been reported in the most severe forms of ectodermal dysplasia. Agenesis of teeth is rare in the human primary dentition. When it occurs, it is usually in the incisor region (Stewart et al, 1982).

In the permanent dentition, hypodontia is most commonly seen in the third molars with a frequency of around 10 - 25 percent in Caucasian populations (Stewart et al, 1982). However, extensive racial variation is observed. In African negroes and Australian aborigines, the prevalence of persons lacking one or more third molars is approximately only 1 percent whereas in Japanese

population the prevalence is around 30 percent (Arita and Iwagaki, 1963).

Apart from the third molars, the mandibular second premolar appears to be the most commonly missing tooth (Horowitz, 1966; Blayney and Hill, 1967; McKibben and Brearley, 1971), although a couple of studies have shown that the maxillary lateral incisor is the most frequently missing tooth (Muller, 1970; Werther and Rothenberg, 1939). However, most studies have indicated that the permanent maxillary lateral incisor is the second most commonly missing tooth after the mandibular second premolar (Byrd, 1943; Clayton, 1956; Grahnen, 1956; Brown, 1957; Glenn, 1961; Rose, 1966; McKibben and Brearley, 1971). A few studies have suggested that the maxillary second premolar is more commonly missing than the maxillary lateral incisor (Dolder, 1937; Gimnes, 1964; Castaldi, 1966; Horowitz, 1966; Blayney and Hill, 1967).

The differences in the reported frequencies of commonly missing permanent teeth are probably related to differences in sample size, racial variation as well as to lack of use of dental radiology in the diagnosis of hypodontia in some studies.

Systemic syndromes showing hypodontia include ectodermal dysplasias (Smith, 1982), Down syndrome (Barden, 1983), Rieger syndrome (Gorlin et al, 1978) and the Nance-Horan syndrome (Seow et al, 1985a).

Supernumerary teeth

Supernumerary teeth in the primary dentition are rare, being seen in approximately 0.5 percent of children (Grahnen and Granath, 1961) and are most frequently located in the maxillary anterior region. In the permanent dentition, they are most frequent in the maxilla (9:1), with a sex predilection for males (2:1). Overall, a frequency of between 1 - 3 percent has been observed for Caucasians (Stewart et al, 1982).

Multiple supernumerary teeth are commonly associated with certain disorders e.g. cleidocranial dysplasia (Hutton et al 1981) and Gardner syndrome (Stewart et al, 1982), both of which are autosomal dominant syndromes. Supernumerary teeth have also been occasionally reported in Hallermann-Streiff (Gorlin et al, 1978) and orofaciodigital syndromes, as well as in cleft lip and palate patients (Smith, 1982).

Abnormalities of tooth morphology

Morphological abnormalities of the teeth may be classified into abnormalities of tooth size, crown abnormalities and root abnormalities.

Abnormalities of tooth size

Microdontia describes teeth smaller than the usual limits of variation while macrodontia refers to teeth larger than normal.

These conditions may involve a single tooth or the entire dentition. In addition, the morphological changes may be further classified into (i) true generalised states where the jaws are normal in size and the teeth abnormal, and (ii) relative generalised states where the teeth appear abnormally large or small due to the jaws being abnormal in size (Shafer et al, 1974).

Crown abnormalities

Crown abnormalities consist of a diverse group of abnormalities ranging from axial core defects to conjoined teeth. Axial core defects include dens-in-dente or dens invaginatus where a lingual invagination of enamel, dentine and pulp occurs as a result of an early invagination of the enamel epithelium. The condition is most commonly found in the permanent maxillary lateral incisors and occurs in about 1.8 - 5.1 percent of Caucasians but is rare in Negroes (Shafer et al, 1974; Gotoh et al, 1979; Rakes et al, 1988).

Another axial core defect is dens evaginatus in which a cone-shaped tubercle consisting of enamel, dentine and pulp is situated in the central groove or lingual ridge of the buccal cusp of a permanent molar or premolar. Den evaginatus is rare in the Caucasian populations but in Asiatic races is found in a prevalence of about 1 - 4 percent (Reichart and Tantiniran, 1975; Chen, 1984).

Conjoined teeth occur in many forms and degrees of union, and may be found in both primary and permanent dentitions. It may result

from an abortive attempt by a single tooth to divide and is due to the invagination of the developing dental organ (Stewart et al, 1982). Twinning indicates the cleavage is complete, resulting in the formation of a supernumerary tooth which is a mirror image of its counterpart. In fusion, two normally discrete dental organs fuse, resulting in a large single tooth. The prevalence of fusion ranges from 0.5 percent in Caucasian populations (Stewart et al, 1982) to about 5 percent in Japanese (Saito, 1959).

Root abnormalities

Root shapes vary significantly among the races with Mongoloid roots being simpler in form compared to those of Indo- European races (Stewart et al, 1982). In addition, division of premolar roots into multiple structures is most common in the Bantu races (Barker, 1973).

An unusual root morphology known as taurodontism as well as accessory furcation root canals in molars will be reviewed in the following section.

Taurodontism

Introduction

Although teeth with a cylindrical or prismatic shape were first described in prehistoric hominids by German authors, Pickerill (1909) was the first to observe this dental anomaly in modern man.

He called the affected teeth "radicular dentomata".

A few years later, Keith (1913) coined the term "taurodontism" to describe the unusual molars of Neanderthal human fossils found near Heidelberg, Krapina, Jersey, Spy and Gibraltar. The origin of this term is from the Greek "tauros" meaning "bull" and "odontos" meaning "tooth". This term was so chosen because Keith observed that the condition resembled the dentition in the ox. To describe the opposite condition as seen in the teeth of the carnivore, Keith used the term "cynodontism" or dog-like teeth.

Witkop (1971) defined taurodontism in descriptive terms: "Taurodont teeth have pulp chambers in which the bifurcations or trifurcations are displaced apically so that the chambers have greater apico-occlusal heights than in cynodont teeth and lack constrictions at the level of the cementoenamel junctions. The distances from the bifurcations or trifurcations of the roots to the cementoenamel junction are greater than the occlusal-cervical distances".

Because there are many degrees of severity in the manifestation of taurodontism, Shaw (1928) subjectively classified this condition into 3 subtypes: hypotaurodontism (minimally affected), mesotaurodontism (moderately affected), hypertaurodontism (severely affected).

Prevalence of taurodontism

The true prevalence of taurodontism reported in modern populations is difficult to ascertain accurately due to lack of valid, standardised diagnostic criteria. In the primary dentition, taurodontism has been reported in 0.54 percent in Japanese children (Daito and Hieda, 1971). In the permanent dentition, the prevalence has been found to vary from 0.57 percent in a North American Caucasian population (Witkop, 1971) to 6.9 percent in an English sample (Holt and Brook, 1979). Studies with large population groups include that of Blumberg et al (1971) which found 2.5 percent of nearly 12,000 individuals affected. Also, Studt (1972) examined 5,000 dental patients and noted the condition in 0.9 percent. In contrast, a high prevalence of 5.6 percent taurodontism was observed in the study by Shifman and Chanannel (1978) on Israeli adults.

Accessory furcation canals in molars

The existence of lateral or accessory canals communicating from the pulp to the periodontal tissues has been recognised for a long time (Coolidge, 1929; Seltzer et al, 1963; Gutmann, 1978). These canals represent potential pathways of spread of inflammation from the pulp to the periodontal tissues causing loss of periodontal attachment. In addition, in primary molars, furcation canals have added clinical significance due to the succedaneous premolars being in close apposition to the furcal region. Thus, these teeth may be damaged through infection or pulpal medicaments spreading through these canals.

Most studies on the anatomy of the furcation region have centred on the permanent dentition. Early attempts to study the internal anatomy of the pulp were unsatisfactory due to inadequate techniques (Hess, 1925).

With the introduction of improved methods for the perfusion of pulpal blood vessels for study of pulp vasculature, Kramer (1960) as well as Saunders (1966) were able to show that in the furcation areas of molars were found large and small vessels traversing to supply root canals.

In a variation of the above technique, the root canal systems of permanent molars were infused with dye so that foramina in the furcation could be identified. An advantage of this method is that patency of these canals can also be ascertained. Employing this technique, Lowman et al (1973) showed that 59 percent of 46 permanent molars exhibited patent furcation canals. Similarly, Vertucci and Williams (1974) demonstrated that 46 percent of 100 mandibular molars had accessory canals in the furcation region, and Gutmann (1978) found a prevalence of 24 percent in 102 teeth.

Using serial histological studies on abscessed molars, other workers (Rubach and Mitchell, 1965; Seltzer et al, 1963) also demonstrated that accessory canals occurred commonly in the bifurcation or trifurcation regions of molars.

In addition, topographical studies using scanning electron microscopy by Koenigs et al (1974), as well as Burch and Hulen

(1974) have further confirmed the presence of numerous accessory foramina in the furcation of permanent molars. Although the patency of such foramina between the pulp chamber and external root surface is not established, Burch and Hulen (1974) observed that as many as 76 percent of the molars studied showed multiple foramina in the furcation area. However, these results were disputed by a more recent scanning electron microscopic investigation (Perlich et al, 1981) which showed that only 5 out of 62 molars (8.1 percent) had accessory foramens ranging in size from 7 to 250 μm in diameter.

CHAPTER TWO

INCREASED PREVALENCE OF DEVELOPMENTAL DENTAL DEFECTS IN
LOW BIRTHWEIGHT, PREMATURELY-BORN CHILDREN:
A CONTROLLED STUDY

INTRODUCTION

Defects of the enamel can result from various disturbances during amelogenesis. These defects may manifest as surface breaks and decreased enamel thickness known as enamel hypoplasia. Alternatively, the defect may be evident as an abnormality of the translucence of enamel known as enamel opacity. Clinically these enamel defects may present with problems of aesthetics. In addition, enamel hypoplasia may predispose to plaque accumulation and caries, and in severe cases even space loss and malocclusion. There is evidence that enamel defects occur with a very high frequency in prematurely-born children. As early as 1936 Stein reported that 5 of 12 prematurely born children had enamel hypoplasia (Stein 1947). Later studies revealed markedly discrepant prevalences varying from 20 to 100 percent (Grahnen and Larsson 1958; Via and Churchill 1959; Rosenzweig and Sahar 1962; Grahnen et al. 1969; Funakoshi et al. 1981; Mellander et al. 1982; Johnsen et al. 1984; Seow et al. 1984a, 1984b). *100126101, 1992*

While the pathogenesis of the dental defects remains unclear, it is probable that both systemic disturbances and local factors contribute to the aetiology. In the author's previous study of prematurely-born children with neonatal rickets derangement of calcium metabolism as a possible systemic factor in the pathogenesis of dental defects was identified (Seow et al. 1984b). In addition it was found that local traumatic factors such as laryngoscopy and endotracheal intubation applied during

the neonatal period may contribute to the aetiology of these defects (Seow et al. 1984a). With decreasing birthweight there is greater propensity for systemic illness and the likelihood of endotracheal intubation increases. Hence it is likely that the lower the birthweight, the greater the prevalence of enamel defects. In this study, the author attempts to further delineate the causes of enamel defects in prematurely born children by studying the prevalence of enamel defects in 3 groups of children with different birthweights: very low-birth-weight (VLBW, < 1500 g); low-birth-weight (LBW, 1500-2500 g); and normal birthweight (> 2500 g). This classification of newborn birthweights is an accepted standard recommended by the American Academy of Pediatrics (Silverman 1967).

PATIENTS AND METHODS

The children in the VLBW group (< 1500 g) were those born in the period 1983-1985, and were attending the Growth and Development Clinic of the Mater Children's Hospital, South Brisbane. This clinic was established in 1978 to provide a multidisciplinary longitudinal follow-up of all infants of low birthweights managed at the Mater Mothers' Hospital. Children in the LBW group (1500-2500 g) and the normal birthweight group (> 2500 g) were selected at random from the birth register at the same hospital. These children were born at the same time period as those in the VLBW group. One hundred and fifty-seven (97.0%) of

the 162 children whose parents the authors were able to contact consented to the study. The mean (\pm SD) ages of all the children in the study at the time of examination was 25.6 ± 9.1 months (range 9-42 months).

The VLBW group was comprised of 77 children (31 males, 46 females). The mean birthweight was 1177 ± 193 g (range 783-1499 g) and their mean gestational age was 29.4 ± 2.5 weeks (range 22-33 weeks). Thirty (37.7%) of these children were intubated during the neonatal period while 47 were not.

The LBW (1500-2500 g) was comprised of 33 subjects (14 males, 19 females). Their mean birthweight was 2175 ± 273 g (range 1577-2480 g) and their mean gestational age was 36.8 ± 2.2 weeks (range 32-41 weeks). None of the children in the LBW group were intubated.

In the normal birthweight group (> 2500 g) 47 children (25 females, 22 males) were available for study. They were all products of full-term pregnancies and their mean birthweight was 3360 ± 450 g (range 2510-4045 g). None of these children were intubated during the neonatal period.

The dental examinations were performed under ideal conditions at the University Dental School. The teeth were dried and a mirror and probe used to detect dental caries, opacities, and enamel hypoplasia. The diagnosis of opacity was restricted

to teeth with white or yellow brown areas that did not have hypoplastic enamel, i.e., pitting, ridging, or other disturbances of surface contour. If a tooth showed both opacity and hypoplasia, a diagnosis of hypoplasia was made. All clinically observable tooth surfaces were examined and all dental defects were recorded in a comprehensive chart. Intraoral photographs were taken in some children. Postnatal medical and dental histories were obtained from the parents. Maternal and neonatal medical histories were obtained from hospital records.

The Chi-square test was used for statistical analysis of the data.

RESULTS

Prevalence of Enamel Hypoplasia

Table 2.1 shows the prevalence of enamel hypoplasia in the 3 groups of subjects. In the VLBW group, 48 of 77 children showed at least one tooth with enamel defects, giving a prevalence of 62.3 percent. Of these, 8 children (10.4%) had enamel opacities alone and 40 (51.9%) had enamel hypoplasia with or without opacities. However, in the LBW group a much lower prevalence of 27.3 percent was obtained (9 of 33 children affected). In the normal birthweight group of children there was a much lower prevalence of 12.7 percent where only 6 of 47 children were affected. Of these, only 3 children (6.4%) had opacities alone. The difference in prevalence among the 3 study groups is

Table 2.1 The prevalence of enamel hypoplasia in children with very-low (VLBW), low (LBW) and normal birthweights.

Group	Birthweight (g)	Prevalence of Enamel Defects		
		Mean \pm S.D.	Opacities	Hypoplasia Total
VLBW (n=77)	1177 \pm 193	8 (10.4%)	40 (51.9%)	48 (62.3%)
LBW (n=33)	2175 \pm 273	2 (6.1%)	7 (21.2%)	9 (27.3%)
Normal (n=47)	3360 \pm 450	3 (6.4%)	3 (6.4%)	6 (12.7%)

The difference in prevalence of enamel defects in the 3 groups is statistically significant ($\chi^2 = 57.7$, $df = 2$, $p < 0.001$).

statistically significant ($P < 0.001$), indicating that prevalence of enamel hypoplasia varies in direct relation to birthweight.

Distribution of Enamel Hypoplasia

The author also analyzed the distribution of enamel hypoplasia in the 3 groups of children for possible insight into the aetiology of the dental defects. Table 2.2 shows the distribution of enamel hypoplasia in the study groups. In the VLBW group 63.1 percent of all affected teeth occurred on the left side compared with 36.9 percent on the right side. This difference was statistically significant ($P < 0.005$). In contrast, in both the low and normal birthweight groups, the dental defects appeared fairly evenly distributed on both left and right sides ($P > 0.1$).

The increased numbers of affected teeth on the left side in the VLBW group is most likely related to trauma from laryngoscopy and endotracheal intubation which affect mainly maxillary anterior teeth (Seow et al. 1984a). In order to determine this, the distribution of affected maxillary anterior teeth in intubated and non-intubated children in the VLBW group were analyzed. As shown in Table 2.3, the intubated children showed a twofold increase in numbers of affected teeth on the left side compared to the right (67.2 percent of all affected maxillary teeth vs. 32.8 percent, $P < 0.005$). In contrast, in the non-intubated group, there was no difference in distribution of

Table 2.2 The distribution of enamel hypoplasia in children with very-low (VLBW), low (LBW) and normal birthweights.

Birthweight	Affected teeth (percent of total)		
	Left sided	Right sided	p value
VLBW (<1500g)	63.1	36.9	<0.005
LBW (1500-2500g)	58.3	41.7	>0.1
Normal (>2500g)	52.2	47.8	>0.1

Table 2.3 Distribution of affected maxillary anterior teeth (incisors and canines) in 47 intubated and 30 non-intubated VLBW children.

Affected maxillary anterior teeth (% of total)			
	Left	Right	p value
Intubated	67.2	32.8	<0.005
Non-intubated	53.8	46.2	>0.1

affected teeth between the left and right sides (53.8 percent vs. 46.2 percent, $P > 0.1$).

DISCUSSION

Previous studies of prematurely-born, low birthweight children have indicated a high overall prevalence of dental defects ranging from 20 to 100 percent (Stein 1947; Grahnen and Larsson 1958; Via and Churchill 1959; Rosenzweig and Sahar 1962; Grahnen et al. 1969; Funakoshi et al. 1981; Mellander et al. 1982; Johnsen et al. 1984; Seow et al. 1984a, 1984b). However, most of these studies were done on isolated groups without normal birthweight control children or poorly selected controls. Table 2.4 shows the summary of clinical studies on prematurely-born children which included children with normal birthweights. As can be seen from the table, the prevalence of dental defects in LBW children in these studies is around 30 percent. The present study gives a comparable figure of 27.3 percent for this birthweight group. In the VLBW group, however, prevalence figures are comparatively higher. In the study of Johnsen et al. (1984), there was a prevalence of enamel defects of 52 percent. In the present study, the prevalence for the VLBW group is slightly higher, at 62.3 percent

A major difference between this study and previous studies lies in the prevalence of dental defects in normal birthweight

Table 2.4 Analysis of studies on the prevalence of enamel defects in prematurely-born children which included children with normal birthweights.

Study	Birth Weight	Percent ⁺ Acceptance	Prevalence of Enamel Defects*
Grahnen & Larsson, 1958	LBW Normal	87.1 77.2	32.1 13.1
Rosenzweig & Sahar, 1962	LBW Normal	N.R. N.R.	23.8 1.2
Mellander et al, 1984	LBW Normal	72.2 30.9	30.7 39.6
Johnsen et al, 1984	VLBW Normal	N.R. N.R.	52.0 26.0
Seow et al (this study)	VLBW LBW Normal	100 100 97	62.3 27.3 12.8

N.R. - not reported

* - Enamel defects include both enamel hypoplasia and opacities

+ - denotes $\frac{\text{number studied}}{\text{number approached}} \times 100$

children. In the present study, this prevalence is 12.8 percent, a figure close to that of the study by Grahnen and Larsson (1958). However, Mellander et al. (1982) and Johnsen et al. (1984) reported exceptionally high prevalence rates of 39.6 percent and 26 percent respectively. The reasons for this gross discrepancy may be due to (1) the use of subjects from a clinic population as in the study of Johnsen et al. (1984), or (2) sampling error from low acceptance rates as in the study of Mellander et al. (1982).

The reasons for the difference in prevalence of enamel hypoplasia in the various birthweight groups are most likely related to both systemic and local factors. Children with the most premature births and lowest birthweights have the highest tendency to suffer from systemic derangements which can affect dental development adversely. Enamel hypoplasia resulting from systemic disturbances usually involve several teeth as shown in Figure 2.1. These systemic factors include neonatal asphyxia (Grahnen et al. 1969), respiratory distress syndrome (Funakoshi et al. 1981; Mellander et al. 1982; Johnsen et al. 1984) maternal pre-eclampsia (Via and Churchill 1959), maternal diabetes (Grahnen and Edlund 1967; Tsang et al. 1973), hyperbilirubinemia (Grahnen and Granath 1962; Funakoshi et al. 1981), and neonatal infection (Funakoshi et al. 1981).

A previous study of a group of prematurely-born, VLBW children with neonatal rickets showed that every one was affected



Fig. 2.1 Enamel hypoplasia resulting from systemic disturbances usually involve several teeth.

by enamel malformation (Seow et al. 1984b). As rickets is a major disturbance in calcium metabolism, it is not surprising that such a high prevalence of enamel defects is noted. In fact, all prematurely-born children suffer from low calcium stores and disturbed calcium metabolism, with the lowest birthweight children most severely affected (Tsang et al. 1973; Tsang 1983). Other perinatal factors associated with prematurity such as hypoxia, sepsis, cerebral injuries, and hyperbilirubinaemia may also indirectly cause disturbances in calcium metabolism (Tsang et al. 1983). It is possible that through this mechanism many systemic factors cause enamel hypoplasia in prematurely-born children.

Local factors also contributed to the differences in prevalence of enamel hypoplasia in the 3 study groups of children. Children with the lowest gestational ages and birthweights tend to suffer most from respiratory problems in the neonatal period and have the greatest need for laryngoscopy and endotracheal intubation. These traumatic procedures have been associated with enamel hypoplasia of the maxillary teeth (Moylan et al. 1980; Wetzel 1980). A previous study has shown that children who underwent laryngoscopy and endotracheal intubation in the neonatal period had a fourfold increase in prevalence of defects of the maxillary anterior teeth compared with non-intubated children (Seow et al. 1984b). In addition, these defects occurred mainly on the left maxillary anterior teeth, suggesting left-sided pressure from the laryngoscope blade (Fig 2.2). The



Fig. 2.2. Some defects occurred mainly on the left maxillary anterior teeth suggesting left-sided pressure from the laryngoscope blade.

present study confirms the author's previous observations. Only the VLBW group, which included intubated children, demonstrated an increase in dental defects on the left side, confirmed by analysis of the distribution of defects on the anterior maxillary teeth.

CHAPTER THREE

**MINERAL DEFICIENCY IN THE PATHOGENESIS OF ENAMEL HYPOPLASIA IN
PREMATURELY-BORN VERY LOW BIRTHWEIGHT CHILDREN**

INTRODUCTION

Reports on the prevalence of developmental dental defects in prematurely-born, low birth-weight children vary widely from 20-100 percent (Grahnen and Larsson, 1958; Rosenzweig and Sahar, 1962; Johnsen et al, 1984; Mellander et al, 1982; Seow, 1986; Seow et al, 1984a; 1984b; 1987). With increasing survival of very low birthweight (VLBW, <1500g) infants in recent years, studies are now available on the dentition of such children. In a controlled study, the author found that the lower the birth-weight of a prematurely-born child, the greater is his/her tendency to develop enamel defects (Seow et al, 1987).

Although the pathogenetic mechanisms of these dental defects are still unclear, it is likely that both local and systemic causes are involved. An important local factor is trauma from laryngoscopy and endotracheal intubation which usually results in localised enamel hypoplasia, involving only the left maxillary anterior teeth (Seow et al, 1984a; 1987). Systemic causes associated with enamel hypoplasia include rickets of prematurity (Seow et al, 1984b), respiratory distress (Johnsen et al, 1984), neonatal asphyxia (Grahnen et al, 1969), maternal pre-eclampsia (Via and Churchill, 1959) maternal diabetes (Grahnen and Edlund, 1967), hyperbilirubinemia (Grahnen and Granath, 1962; Funakoshi et al, 1981) and neonatal infection (Funakoshi et al, 1981).


Although significant associations have been found between individual medical conditions and enamel defects, it is difficult to isolate the relative importance of each medical condition since many of them occur concurrently in VLBW prematurely-born children. Moreover it is likely that many of these systemic disturbances act through a common mechanism of decreased mineral stores which may directly affect mineralization of dental tissues (Seow et al, 1984b). Osteopenia or under-mineralization of bone is a well recognised complication of prematurity (Tsang et al, 1973; Tsang, 1983; Brooke and Lucas, 1985; Chesney et al, 1981; Steichen et al, 1980; Kooh et al, 1977). It is likely that factors associated with osteopenia in the VLBW prematurely-born children are also those involved in the pathogenesis of enamel hypoplasia commonly seen in these children.

This comparative study was conducted to determine if mineral deficiency as evidenced by radiological demineralization, is associated with enamel hypoplasia in a group of VLBW children.

PATIENTS AND METHODS

Patients

The study patients attended the Growth and Development Clinic at the Mater Children's Hospital which was established in 1978 to provide multidisciplinary longitudinal follow-up of VLBW children. Forty-five children with a mean birthweight of 1149 ± 191 g and a mean gestational age 29.4 ± 2.3 wks and adequate

radiological records taken during the neonatal period were selected for study. The mean (\pm SD) ages of all the children at the time of dental examination was 30.0 ± 9.1 mo (range 18-42 mo) 

The dental examinations were performed at the University Dental School. Informed consent was obtained from parents for participation in the study. The teeth were dried and a mirror and probe used to detect dental caries, opacities and enamel hypoplasia. A diagnosis of enamel hypoplasia was made if there was a break in the continuity of the enamel surface such as pitting, ridging, or other disturbances of surface contour (Commission on Oral Health, FDI, 1982). Enamel opacities were diagnosed as changes in the translucency of enamel e.g. white, brown or yellow areas without breaks in the continuity of the enamel surface. If a tooth showed both opacity and hypoplasia, a diagnosis of hypoplasia was made. All clinically observable tooth surfaces were examined and all dental defects were recorded in comprehensive charts. Intraoral photographs were taken in some children. Postnatal medical and dental histories were obtained from the parents and maternal and neonatal medical histories were obtained from hospital records.

Radiological Measurements of Cortical Bone

Mineral deficiency in the VLBW infants may be assessed by the degree of skeletal bone mineralization (Garn et al, 1971; Poznanski et al, 1980; Cameron et al, 1968). In this study, bone

mineralization was determined by measuring the cortical area of the humerus according to the method of Poznanski et al (1980).

Radiological measurements were performed retrospectively by a radiologist (J.P.M.) who was unaware of the dental examination results. Chest radiographs which included the upper half of the humerus were used. These were taken during the neonatal period. In the method of Poznanski et al (1980), the cortical thickness and area were obtained above the point where the nutrient foramen enters the humerus (Fig. 3.1). The outer (T) and inner (M) diameters of the humerus were taken with a direct-reading caliper, and the cortical thickness (C) was determined using the formula $C = T - M$. The cortical area (CA) = $\pi/4 (T^2 - M^2)$ was also calculated. Inter and intra-examiner reliability of the method were already established in the well-regarded publication by Poznanski et al (1980).

The radiographs used were taken at a mean age of 10.7 ± 7.5 days (range 1-27 days). Although the radiographs were taken at varying times during the neonatal period, the values for cortical area have been shown to be fairly constant for any particular patient up to 60 days postnatal (Masel et al, 1982). In some patients several radiographs were available. In these cases, a mean value of all the cortical areas was obtained.



Figure 3.1 Radiograph showing where the cortical thickness of the humerus was measured. This is just above the point where the nutrient canal enters the humerus (arrow).

Statistical Analysis

The student's t-test, Chi-square test, or the Fisher's exact test, where appropriate, were used for statistical analysis of the data.

RESULTS

Prevalence of enamel hypoplasia

Of the 45 children examined, 31 (68.9 percent) demonstrated enamel hypoplasia (Table 3.1). Thirteen of these 31 children (28.9 percent) had enamel hypoplasia localised to the left primary maxillary central and/or lateral incisor and canine. A further 18 (40.0 percent) children showed generalised enamel hypoplasia involving usually all the primary maxillary incisors, and occasionally the canines. In 14 (31.1 percent) children, no enamel defects were evident.

Prevalence and type of enamel hypoplasia observed in intubated and non-intubated children

Although it had been previously established that laryngoscopy and endotracheal intubation is associated with localised enamel hypoplasia (Seow et al, 1984a, 1986) the prevalence of each type of defect in intubated and non-intubated children has not previously been described. This was therefore analysed in the present study.

As shown in Table 3.1, 41.9 percent of intubated children showed localised enamel hypoplasia, 25.9 percent generalised

Table 3.1. Prevalence of enamel hypoplasia

	Intubated (n=31)		Non intubated (n=14)		Total (n=45)	
	No.	% of intubated	No.	% of non- intubated	No.	% of total
No defect (n=14)	10	(32.2%)	4	(28.6%)	14	(31.1%)
Enamel Hypoplasia						
Localised enamel hypoplasia (n=13)	13	(41.9%)	0		13	(28.9%)
Generalised enamel hypoplasia (n=18)	8	(25.9%)	10	(71.4%)	18	(40.0%)

The differences in prevalence of enamel hypoplasia between intubated and non-intubated children were statistically significant, $p=0.002$ (Fisher's exact test).

enamel hypoplasia and 32.2 percent no defect. In contrast, in the non-intubated group of children, none showed localised enamel hypoplasia, 71.4 percent had generalised enamel hypoplasia and no defect was observed in 28.6 percent. These differences were statistically significant ($p=0.002$, Fisher's exact test), indicating that localised enamel hypoplasia is strongly associated with intubation, whereas generalised enamel hypoplasia is observed in fairly equal frequencies in both intubated and non-intubated groups.

Correlation of enamel hypoplasia with bone cortical area

The mean humeral cortical areas in the groups of children with and without enamel hypoplasia were compared. As shown in Table 3.2, there were no statistically significant differences in the mean birthweights or gestational ages in these two groups of children. Hence it is appropriate to compare their mean cortical areas directly (Poznanski et al, 1980).

To validate this further, a statistical score was computed for the cortical area of a patient in relation to the standard curve for his/her gestational age. The scores were as follows: 9 for $> +2$ S.D., 8 for $+1.5$ S.D., 7 for $+1$ S.D., 6 for $+0.5$ S.D., 5 for mean, 4 for -0.5 S.D., 3 for -1 S.D., 2 for -1.5 S.D., 1 for < -2 S.D. As shown in Table 3.2 the mean score for cortical area in children with enamel hypoplasia was low, at 4.1 ± 1.4 (i.e. at -0.5 S.D. of the normal curve) compared to a high of 7.5 ± 1.2 (i.e. between $+1$ S.D. and $+1.5$ S.D. of the normal curve) in

Table 3.2. Association of enamel hypoplasia with decreased cortical thickness

	Enamel Hypoplasia			p value
	Generalised (n=18)	Localised (n=13)	Without Enamel Hypoplasia	
Gestational Age (weeks) (Mean \pm SD)	29.0 \pm 2.3	29.6 \pm 2.4	28.4 \pm 2.7	>0.1
Birthweight (g) (Mean \pm SD)	1132 \pm 224	1101 \pm 203	1179.5 \pm 183	>0.1
Cortical Area (mm ²) (Mean \pm SD)	9.9 \pm 2.0	10.4 \pm 1.7	13.9 \pm 1.4	<0.001
Score for Cortical Area (Mean \pm SD)*	3.9 \pm 1.6	4.1 \pm 1.4	7.5 \pm 1.2	<0.001

* This statistical score was computed for the cortical area of a patient in relation to the standard curves for his/her gestational age. The scores were as follows. 9 for >+SD; 8 for +1.5 SD; 7 for +1 SD; 6 for +0.5 SD; 5 for mean; 4 for -0.5 SD; 3 for -1 SD; 2 for -1.5 SD; 1 for <-2 SD.

children without enamel hypoplasia. This difference is statistically significant, $p < 0.001$, indicating that children with enamel hypoplasia tended to have lower cortical areas compared to children without enamel defects.

Comparison of children with localised and generalised enamel hypoplasia

Although localised enamel hypoplasia has been associated with local aetiological factors, it is of interest to compare children with this form of enamel hypoplasia with those showing the generalised form to determine if there are differences in systemic susceptibility. No significant differences can be detected between these two groups of children in their gestational ages and birthweights (Table 3.2). More importantly, their mean cortical areas do not differ significantly (9.9 ± 2.0 vs 10.4 ± 1.7) with both statistical scores for cortical mass at about 1 S.D. below the mean. These results indicate that both localised and generalised enamel hypoplasia are associated with a significantly lower mean cortical mass.

Comparison of cortical areas in intubated children with and without enamel hypoplasia

Since not all intubated children demonstrate enamel hypoplasia, the question posed was whether intubated children with enamel hypoplasia also have lower mean cortical areas compared to those without enamel defects. The results (Table 3.3) showed this to be true, indicating that children with lower cortical masses are those most susceptible to the local traumatic effects of intubation.

Table 3.3. Comparison of cortical areas in intubated children with and without enamel hypoplasia.

	Mean Cortical Area ($\text{mm}^2 \pm \text{SD}$)
Intubated children with enamel hypoplasia (n=21)	10.0 \pm 1.8
Intubated children without enamel hypoplasia (n=10)	12.4 \pm 1.5

The difference between the 2 groups of intubated children is statistically significant, $p < 0.001$. ($t = 3.75$, $df = 30$).

DISCUSSION

The VLBW prematurely-born infant usually suffers a multitude of serious illnesses during the neonatal period such as respiratory distress, apnoea, hypoglycaemia, intracranial haemorrhage, cardiac defects and infections. The high prevalence of enamel hypoplasia in this group of children has been associated with many such conditions individually (Johnsen et al, 1984; Grahnen and Granath, 1962; Funakoshi et al, 1981). However, significant associations of individual medical conditions and enamel hypoplasia are not difficult to obtain from statistical computations when low birthweight children with enamel hypoplasia are compared with healthy full-term control children without any enamel defects. The difficulty therefore, lies in defining the relative importance of these conditions in the pathogenesis of enamel defects. Multivariate analyses are often difficult in these cases due to nearly all the conditions occurring concurrently in most of the patients showing enamel defects.

Rather than attempting to discern which individual medical conditions are most important, we have examined a possible central mechanism by which many of these conditions may operate to cause enamel hypoplasia in the VLBW children. This is mineral deficiency or osteopenia which is diagnosed in our study by measurements of the radiological cortical area of the humerus. Direct measurements of blood calcium levels as indicators of mineral loss are usually not useful as blood calcium levels tend

to remain fairly constant even in cases of extreme calcium deficiency (Masel et al, 1982; Binstadt and L'Heureux, 1978), mineral being removed from calcified tissues to maintain serum homeostasis.

The results of the present study show that children with the lowest mineral stores in bone, i.e. those with cortical areas below the mean for gestational age are most predisposed to enamel hypoplasia. From these results, it is reasonable to hypothesize that in the presence of mineral deficiency, calcification in dental tissues may be decreased or even halted in an attempt to achieve mineral balance in serum. This hypothesis is substantiated by the observation that children with various types of congenital and acquired forms of calcium balance disorders all show enamel hypoplasia (Garfunkel et al, 1979; Hinrichs, 1956; Purvis et al, 1973). In addition, the extreme sensitivity of the ameloblasts to calcium change of even short periods of time is evidenced by the finding that neonatal hypocalcaemia of just a few hours duration is associated with enamel hypoplasia (Purvis et al, 1973; Stimmeler et al, 1973).

Of interest also is the finding from this study that intubated children with enamel hypoplasia had smaller cortical areas compared with intubated children without enamel defects. These results indicate that low mineral stores further predispose intubated children to the effects of local trauma from the laryngoscope.

Metabolic bone disease, manifesting as decreased mineralization of bone in prematurely-born children (Fig. 3.2), is gaining increasing recognition with improving survival figures for infants weighing less than 1000 g (Davis et al, 1978; Lewin et al, 1971). However, the pathogenesis is still unclear and in any one infant, is likely to be multifactorial in nature. The main cause of metabolic bone disease is probably inadequacy of mineral supply to these infants whose requirements for calcium and phosphate are large. Unsupplemented breast milk which supplies only a fraction of the estimated fetal accretion rate of calcium and phosphorus for the last trimester of pregnancy has been thought to be a contributory factor (Abrams et al, 1988). However, many VLBW infants fed on a special preterm formula with twice the phosphorus and calcium concentrations of human milk and receiving a high intake of vitamin D still developed biochemical evidence of metabolic bone disease (Senterre et al, 1983; McIntosh et al, 1983).

Hence other factors apart from mineral supply, may also be involved. One of these may be immaturity of hepatic and kidney vitamin D metabolism (Kovar et al, 1982; Seino et al, 1981). However, there is little evidence that vitamin D deficiency is an important problem. Inadequate placental transfer of calcium and phosphorus may also be a contributory factor since osteopenia has been found to be more prevalent in neonates with maternal histories of pre-eclampsia (Bosley et al, 1980).



Figure 3.2 Radiographs of the humerus of 2 VLBW infants. The left radiograph depicts minimal loss of cortical bone in stark contrast to that on the right which shows advanced demineralization of the cortex.

For prophylaxis against metabolic bone disease it is now common practice to supplement all preterm infants with extra calcium and phosphate and in some instances, vitamin D. All the patients in the present study had been placed on these regimes, yet evidence of osteopenia and enamel hypoplasia were still observed.

Whatever the causes, metabolic bone disease is now considered a common problem of prematurity of birth and low birth-weight. Dental defects associated with it should also be recognised so that early dental referral and management of accompanying clinical problems may be instituted.

CHAPTER FOUR

**DENTAL ERUPTION IN LOW BIRTH-WEIGHT, PREMATURELY-BORN CHILDREN:
A CONTROLLED STUDY**

INTRODUCTION

Several studies on the growth and development of low birth weight, prematurely-born children have indicated that although physical growth disturbances may be present for some time after birth, catch-up growth usually occurs by early childhood (Fitzhardinge, 1976). However, although the physical development of prematurely-born children has been well investigated, there are relatively few studies on the dental development of these children. Our previous investigations supported others showing a high prevalence of enamel defects of about 20-100 percent (Seow et al, 1984a, 1984b, 1989; Grahnen & Larsson, 1958; Mellander et al, 1982; Johnsen et al, 1984).

It is not certain whether dental eruption is affected by prematurity of birth and low birthweight. Early studies were in disagreement as to whether low birthweight children had delayed eruption (Wedgewood & Holt, 1968; Tsubone, 1962). Two later investigations suggested that teething age of the first tooth was delayed in prematurely-born children but eruption of other teeth was not studied (Trupkin, 1974; Golden et al, 1981). This study was designed to detect differences in the tooth eruption status of prematurely-born, very-low-birthweight (VLBW, <1500g) children compared to low-birthweight (LBW, 1500-2500g) and normal birthweight (NBW, >2500g) children in order to determine if dental eruption is affected by low birthweight and prematurity of birth.

PATIENTS AND METHODS

The VLBW children were those attending the Growth and Development Clinic of the Mater Children's Hospital, South Brisbane. This clinic provides a multidisciplinary longitudinal follow-up of all infants of very-low-birthweight managed at the Mater Mother's Hospital. Children in the LBW group and the NBW group were born at the same time period as the VLBW group. They were selected at random from the birth register of the hospital. Parental consent to participate in the study was given by >97 percent of the patients we were able to contact. There were 153 subjects in total, and 97 percent were Caucasian with 3 percent part-Caucasian.

Table 4.1 shows the characteristics of the patients in the study. In the VLBW group, 73 children (30 males, 43 females) were available for study. Their mean gestational age was 29.4 ± 2.5 weeks (range 24-33 weeks) and their mean birth weight was 1179 ± 193 g (range 783-1499g).

In the LBW group (1500-2499g) there were 33 patients, 14 males and 19 females. Their mean gestational age was 37.4 ± 3.1 weeks (range 32-41 weeks) and their mean birth weight was 2176 ± 273 g (range 1577-2480g).

Table 4.1. Some characteristics of the children in the 3 birthweight groups.

Group	Birth Weight (g)	Gestational Age (wks)	*Age at Examination	
			Chronological Age (mths)	Corrected Age (mths)
VLBW (n=73)	1179 \pm 193	29.4 \pm 2.5	24.3 \pm 1.2	21.8 \pm 1.2
LBW (n=33)	2176 \pm 273	37.4 \pm 3.1	25.5 \pm 1.8	25.2 \pm 1.8
NBW (n=47)	3360 \pm 450	40.0 \pm 2.0	30.3 \pm 1.5	30.3 \pm 1.5

* Chronological age indicates true age whereas corrected age indicates chronological age adjusted for the prematurity of birth i.e. Corrected Age = Chronological age - (weeks of prematurity).

In the NBW group (>2500g), 47 children (22 males, 25 females) were available for study. They were all born full-term and their mean birth weight was 3360 ± 450 g (range 2510-4045g).

The ages of the children at the time of dental examination varied from 24.3 ± 1.2 months in the VLBW group to 30.3 ± 1.5 months in the NBW group. This variability in the age at examination is due to the fact that the examinations were extended over a period of time. The corrected age of each child was computed from the chronological (true biological) age using the formula as shown below :

Corrected Age = Chronological age - (weeks of prematurity).

The dental examinations were performed at the University Dental School. All erupted teeth were noted in comprehensive charts. A tooth was considered erupted if any part of its crown had penetrated the mucous membrane. Other abnormalities of the dentition were also noted. Intraoral photographs were taken in some children. Postnatal medical and dental histories were obtained from the parents. Maternal and neonatal medical histories were obtained from hospital records.

It was noted from the histories that no child in the study has had dental extractions or tooth loss from trauma prior to the time of examination.

As the study was a cross-sectional one, as well as not relating to sequence of eruption, the timing of eruption was not studied. Instead, the number of teeth present in each subject was noted with reference to his/her age at the time of dental examination.

Data were coded and computerised, and analysed using analysis of variance (ANOVA) tests to detect statistical differences between groups.

RESULTS

In this cross-sectional study, it was necessary to divide the children into various age groups of 6-11 months, 12-17 months, 18-23 months and 24+ months. This was because the children were examined at different times and it was pertinent to determine whether at any particular age group, a low-birthweight child had significantly less numbers of teeth compared to the child with normal birthweight. These age groups of five-monthly intervals were chosen to include approximately the mean eruption times of the primary incisors, first molars, canines and second molars respectively.

Chronological Age

Table 4.2 shows the mean number of teeth present in each age group of children within each individual birthweight group, using

Table 4.2. Mean number of teeth present in each age group (chronological age) within each birthweight group.

Age Group (mths)	Mean No. of Teeth (<u>±</u> S.E.)		
	VLBW	LBW	NBW
6-11	1.0 <u>±</u> 1.3	3.7 <u>±</u> 1.4	3.0 <u>±</u> 1.8
12-17	6.6 <u>±</u> 0.6	8.0 <u>±</u> 1.3	11.8 <u>±</u> 1.0
18-23	14.0 <u>±</u> 0.6	15.5 <u>±</u> 0.8	14.8 <u>±</u> 0.8
24+	18.7 <u>±</u> 0.4	19.0 <u>±</u> 0.6	18.4 <u>±</u> 0.5

A two-way analysis of variance for the number of teeth for the 3 birthweight and 4 age groups showed a significant interaction between chronological age and birth weight (Table 4.3).

the chronological ages of the children. As can be seen from the table, in the age groups 6-11 months and 12-17 months, the VLBW children had less numbers of teeth compared to the LBW and the NBW children. A two-way analysis of variance for the number of teeth for the 3 birthweight groups and the 4 age groups showed a significant interaction between chronological age and birth weight (Table 4.3) indicating that the lower the birthweight, the less the number of teeth present ($p=0.01$). However, by 18 months, the differences in the number of teeth in the 3 birthweight groups were not significant ($p>0.1$).

Corrected Age

As prematurely-born children are not fully mature at the time of birth, their chronological ages do not correspond to their true biological ages. Hence, a meaningful comparison with full-term, normal children can only be made if the ages of prematurely-born children are corrected for the early births.

Table 4.4 shows the mean number of teeth present in each age group of children within each individual birthweight group using the corrected ages of the children. In contrast to the results using chronological ages of children, a two-way analysis of variance for the number of teeth for the 3 birthweight groups and the 4 age groups showed a non-significant interaction between corrected age and birthweight (Table 4.5).

Table 4.3. Analysis of variance for number of teeth present in the 3 birthweight groups of children using chronological ages.

Source of Variation	Degree of freedom	Sum of Squares	Mean Square	Variance Ratio	'p' value
Age Group	3	3637.9	1212.6	192.5	<0.001
Birthweight group	2	40.1	20.2	3.2	0.04
Age x Birthweight Interaction	6	110.7	18.5	2.95	0.01
Residual	141	882.6	6.3		

The analysis of variance for number of teeth showed a significant interaction between chronological age and birth weight ($S_{6,141} = 2.95$, $p=0.01$).

Table 4.4. Mean number of teeth present in each age group (corrected age) within each birthweight group.

Age Group (mths)	Mean No. of Teeth (<u>±</u> S.E.)		
	VLBW	LBW	NBW
6-11	3.7 <u>±</u> 0.78	5.0 <u>±</u> 1.2	3.0 <u>±</u> 1.8
12-17	9.6 <u>±</u> 0.7	9.0 <u>±</u> 1.8	11.8 <u>±</u> 1.1
18-23	14.1 <u>±</u> 0.6	15.5 <u>±</u> 0.8	14.8 <u>±</u> 0.8
24+	19.0 <u>±</u> 0.5	14.8 <u>±</u> 0.8	18.4 <u>±</u> 0.5

A two-way analysis of variance for the number of teeth for the 3 birthweight and 4 age groups revealed no significant interaction between corrected age and birth weight (Table 4.5).

Table 4.5. Analysis of variance for number of teeth present in the 3 birthweight groups of children using corrected ages.

Source of Variation	Degree of freedom	Sum of Squares	Mean Square	Variance Ratio	'p' value
Age Group	3	3626.4	1215.3	176.1	$p < 0.001$
Birthweight Group	2	6.5	3.3	0.5	> 0.1
Age x Birthweight Interaction	6	39.6	6.6	1.0	> 0.1
Residual	140	956.0	6.9		

The analysis of variance for number of teeth showed no significant interaction between corrected age and birthweight ($S_{6,141} = 0.97$, $p > 0.1$).

DISCUSSION

Various general factors have been suggested to influence dental eruption in the healthy child. These include race, sex and physical development (Friedlaender & Bailit, 1969; Falkner, 1957). Because prematurity of birth and low birthweight may influence general physical development, it is likely that dental development may be similarly affected but few studies have addressed this issue. Most of these previous studies were uncontrolled, and usually only the eruption time of a single tooth examined.

Our present controlled study found that VLBW children have fewer teeth present compared to LBW and NBW children when examined at their chronological ages of 6-17 months, indicating that they have retarded dental eruption at these ages. However, after 17 months, this difference was no longer evident, most probably resulting from "catch-up" growth of the dental and alveolar structures. In relation to this finding is the fact that catch-up growth of general body size has also been documented to occur in low-birthweight, prematurely-born children so that by late childhood, most of these children are comparable in weight and height to their normal birthweight peers (Neligan et al, 1976; Fitzhardinge, 1976).


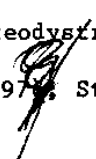
However, our results also indicate that if corrected rather than chronological ages are used in the analysis of data, there

are no significant differences in the mean numbers of teeth in the 3 birthweight groups. This is the case for all the age groups examined. This may indicate that low-birthweight children may be "delayed" in their dental eruption simply because of their birth prematurity per se, and not through delayed dental development. It is suggested that the degree of prematurity i.e. (40 weeks - gestational age) be taken into account when estimating the eruption times of prematurely-born children.

The results of the present study thus confirm and extend that of previous investigators which found that the eruption of the first tooth was delayed in prematurely-born children (Golden et al, 1981; Trupkin, 1974). Also, we did not find any differences in the mean numbers of teeth between the sexes, confirming the results of several other investigators (Falkner, 1957; Roche et al, 1964). In addition our data for NBW children agree with that of Roche et al (1964) in their study of deciduous teeth eruption in Australian children.

Knowledge of normal estimated eruption times of teeth is of clinical importance for accurate diagnosis of various local and systemic conditions that may affect dental eruption. These include supernumerary teeth, impacted teeth, cysts and tumours which may cause local delayed eruption. On the other hand, systemic causes of altered eruption include endocrine disturbances, e.g. hypothyroidism which results in delayed eruption and precocious puberty in which accelerated eruption is observed

(Stewart et al, 1982). In addition, in various abnormalities of the bone there is altered dental eruption. These include cleidocranial dysostosis and Albright hereditary osteodys trophy, both of which show delayed eruption (Miller et al, 1974; Stewart et al, 1982).



Hence the results of the present study is of clinical significance in that prematurely-born children should have their early births taken into account when estimating times for eruption of their dentition.

CHAPTER FIVE

**THE SPECTRUM OF CLINICAL DENTAL MANIFESTATIONS IN VITAMIN
D-RESISTANT RICKETS: IMPLICATIONS FOR MANAGEMENT**

INTRODUCTION

The most common form of rickets in developed countries today is an inherited form of rickets known as vitamin D-resistant rickets (VDRR) (Harrison et al, 1966). This condition, first described by Albright et al. (1937) also is known by various other names such as familial hypophosphataemia, vitamin D-refractory rickets, and phosphate diabetes. The disease is usually inherited in an X-linked dominant manner (Fraser & Sriver, 1976), with an affected male passing the defective gene to all his daughters and none of his sons. In contrast, an affected female will pass the gene to half her daughters and half her sons.

The pathogenesis of VDRR results from a selective disorder of transepithelial transport of phosphate in the kidney, leading to decreased tubular reabsorption of phosphate and persistent hypophosphataemia (Glorieux & Sriver, 1972). The low levels of serum phosphate lead to defective calcification, with signs and symptoms of rickets often appearing at about 8-10 months of age. These signs include lateral bowing of the legs, frontal bossing, enlargement of the costochondral junctions, scoliosis and lordosis. Medical management of VDRR consists of phosphate replacement together with vitamin D given usually in the form of calcitriol.

The dental manifestations of VDRR are quite characteristic, with multiple "spontaneous" dental abscesses being most often reported (Harris & Sullivan, 1960; Archard & Witkop, 1966; Pliskin et al, 1975; Cohen & Becker, 1976; Gardner et al, 1969; Vasilakis et al, 1980; Gallo & Merle, 1979; Seow, 1984a). These abscesses result from pulp exposures which occur easily due to the large pulp chambers usually evident in the dental radiographs of these patients. Histological studies often show abnormal dentine calcification with large calcospherites and tubular defects extending close to the dentino-enamel junction (Harris & Sullivan, 1960; Marks et al, 1965; Archard & Witkop, 1966, Via, 1967).

Although previous studies on patients with VDRR have described the above dental manifestations, little emphasis has been placed on the prevention of dental abscesses. In addition, although it has been reported that hypophosphataemia occurs in varying degrees of severity, it is not known whether dental manifestations are affected accordingly.

The author studied several patients from different families with confirmed diagnoses of VDRR to determine the spectrum of dental manifestations of the disease and the factors associated with these variations. The objective of the study was to provide guidelines in the prevention of dental abscesses which may be a constant problem in affected patients.

SPECTRUM OF DENTAL MANIFESTATIONS

Thirteen patients from 6 different families were studied. A summary of the characteristics of these patients are shown in Table 5.1. Based on dental manifestations and the need for treatment and prevention of dental abscesses, the patients can be divided into 3 main grades as follows.

Grade I is comprised of patients who show minimal or no dental manifestations of VDRR. These patients require only routine dental care and preventive measures. Seven patients in the series can be categorized into this group (Cases 6-13).

Grade II patients are those who show moderate dental manifestations of the disease, only a few teeth are involved, and the prophylactic procedures required are moderate. Four patients in the series can be placed into this group (Cases 3-5).

Grade III is comprised of patients who show severe dental manifestations of the disease and require extensive treatment and aggressive prophylactic measures to prevent the development of dental abscesses. Two patients in the series can be placed into this group (Cases 1 and 2).

Representative cases of each of the above classes are discussed.

Table 5.1 Characteristics of 13 Patients with Vitamin D-Resistant Rickets

Case	Sex	Age at Dental Examination (yrs)	Age of Diagnosis and Start of Medical Treatment	No. of Abscessed Teeth Primary/Permanent		Increased Size of Pulp Chambers	Hypo- plasia of Teeth
1. MG	M	10	4.5 yr	20	1	+++	+
2. SS	M	7	2 yr	16	3	+++	-
3. VB	M	25	2 yr	?	2	++	-
4. SB	F	32	2-3 yr	?	7	+	+
5. NS	F	13	18 mo	3	0	+	+
6. JS	F	25	<12 mo	?	1	-	-
7. KB	F	9	9 mo	0	0	-	+
8. AB	F	2	9 mo	0	-	?	-
9. MB	M	5	9 mo	0	-	+	-
10. WS	F	33	28 yr	?	0	-	-
11. JB	F	35	3 yr	?	0	+	+
12. CB	F	13	9 mo	0	0	-	+
13. TB	F	14	9 mo	0	0	-	-

ILLUSTRATIVE CASES

Grade I (Case 12)

This female patient was 13 years old upon referral to the University Dental School. She was about 9 months old when VDRR was diagnosed and treatment with phosphate and calcitriol started. She inherited the disease from her mother (Case 11). An older sibling (Case 13) also was affected. The family pedigree chart shown in Figure 5.1 revealed typical transmission of the disease in an X-linked dominant manner.

At the time of dental examination, apart from a short stature (height 130.5 cm, 3rd percentile) and slight bowing of the legs, she showed minimal skeletal signs of rickets. Clinical examination revealed that all permanent teeth except third molars were erupted. No caries or periodontal abnormalities were detected but the maxillary right permanent molar showed enamel hypoplasia. No dental abscesses were noted and there was no history of any abscesses in the primary dentition. Radiographic examination revealed normal calcification of enamel and dentine with the pulp chambers fairly normal in appearance (Figure 5.2).

As the teeth were essentially normal, no prophylactic measures for dental abscesses were required. However, fissure sealants were placed on posterior teeth as routine preventive procedures for dental caries.

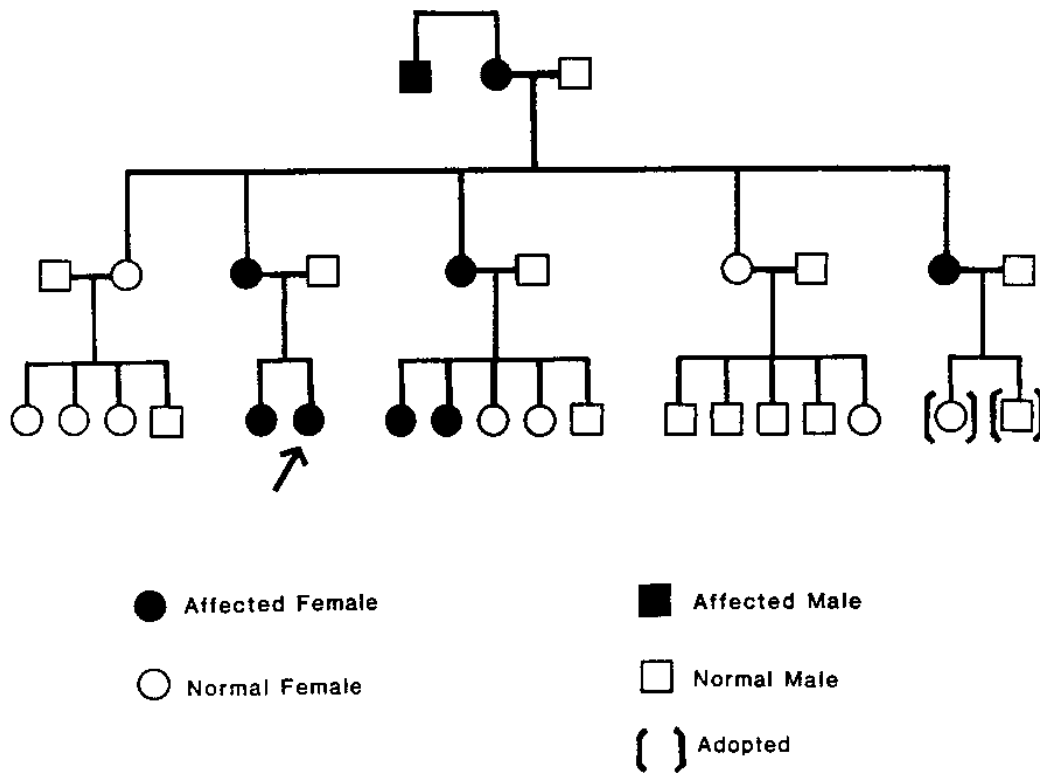


Fig 5.1. Family pedigree of a female (Case 12) affected by VDRR, showing typical transmission of the disease in an X-linked dominant manner. Arrow shows proband.

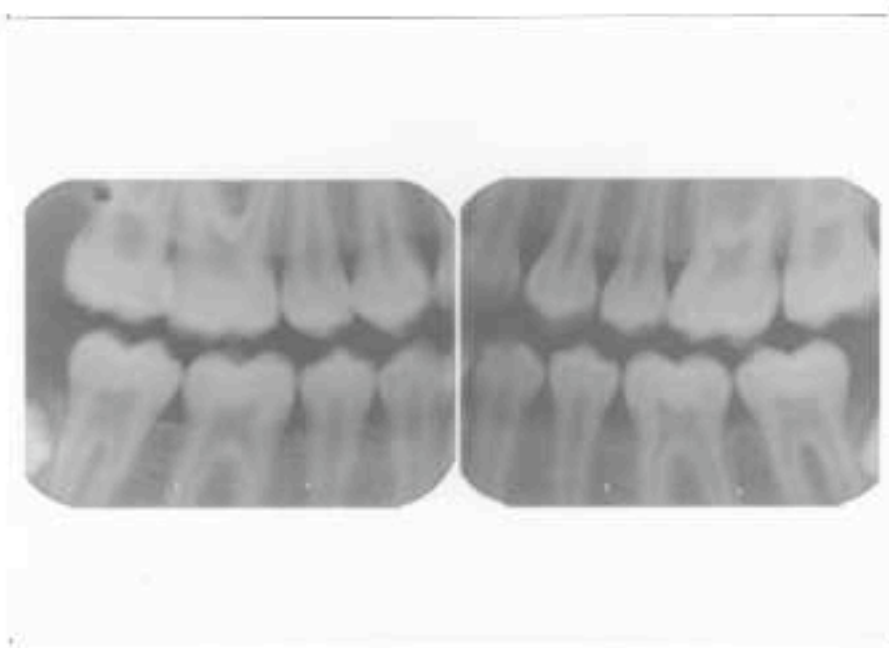


Fig 5.2. Bite-wing radiographs of a female (Case 12) affected by VDRR. The dental manifestations were of Grade 1 severity with near-normal calcification of the teeth. Note normal sizes of the pulp chambers.

The patient's sibling (Case 13) showed essentially similar clinical and radiographic features, with minimal dental signs of VDRR. Of interest, too, is the fact that the mother (Case 11) also exhibited minimal signs of the condition and had no history of dental abscesses despite moderate skeletal manifestations of the disease.

Grade II (Case 5)

This female patient was referred to the Dental School at age 13 years. She was diagnosed as having VDRR at the age of 18 months and had been on phosphate and calcitriol therapy continually. She inherited the disease from her mother (Case 10). Her brother, the only sibling, was unaffected. The mother, who was the first known member of the family with the condition, was diagnosed as having the disease only a few years previously. At the time of dental examination skeletal manifestations of rickets were obvious: bowing of the legs, frontal bossing, and short stature (height 124.8 cm, < 3rd percentile).

At the time of dental examination, all her permanent teeth except the maxillary canines and third molars were erupted. Apart from hypoplasia of the maxillary right central incisor, no abnormalities were detected intraorally. Radiographic examination of the teeth revealed enlarged pulp chambers of all permanent teeth (Fig 5.3).

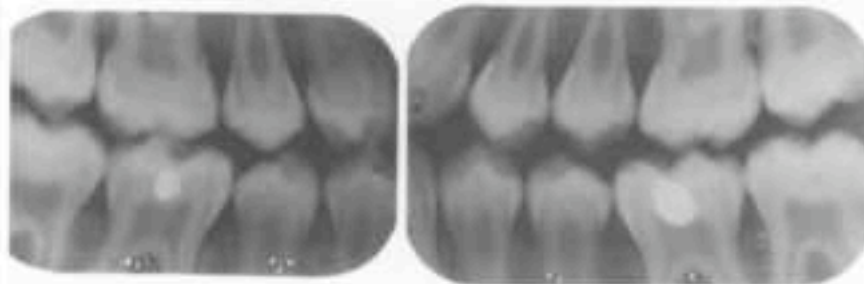


Fig 5.3. Bite-wing radiographs of a female (Case 5) with VIBR. The dental manifestations were of Grade II severity with moderate enlargement of the pulp chambers.

Clinical history confirmed that Case 5 was affected to a lesser degree than Case 1. Although there was a history of 3 "spontaneous" dental abscesses of the primary teeth at the age of 8-9 years, the patient had not experienced an abscess of the permanent teeth by 13 years.

Although this patient was less severely affected compared to Case 1, she still required prophylactic measures to prevent abscesses in predisposed teeth. In this case, occlusal coverage with acid-etched composite resins probably would suffice.

It is interesting to compare this patient with her mother from whom she inherited the condition. The mother had no history of dental abscesses and radiographs (Figure 5.4) showed no abnormalities except for caries. The pulp chambers appeared normal and in spite of the deep occlusal caries on the left mandibular first molar, no apparent abscess had developed.

Grade III (Case I)

The patient, a 10 year-old male, was referred to the University Dental School by his private practitioner at the age of 4 years because of multiple "spontaneous" dental abscesses. There was no family history of rickets. The patient was referred to a pediatrician. He was given vitamin D and oral phosphate supplementation beginning at about age 7. When the patient first was seen by the author at age 9, he showed skeletal signs of rickets with bowing of the legs and frontal bossing of the

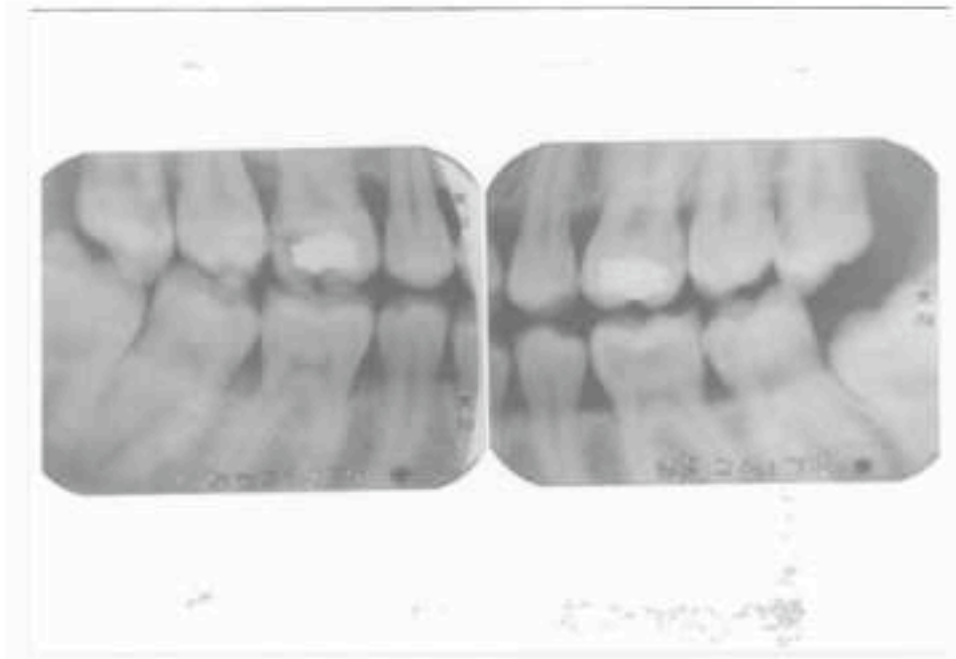


Fig 5.4. Bite-wing radiographs of affected mother of Case 5 taken at initial examination. Although she had VDRR, the dental manifestations were minimal. The pulp chambers of the teeth appeared normal and no abscesses had developed.

skull. His height was 132 cm (25th percentile) and weighed 38 kg (90th percentile).

All immediate family members were healthy and the mother's medical history which included extensive investigations proved negative. It was concluded that the patient's disease may be the result of a fresh genetic mutation.

When the patient first presented to the Dental School at the age of 4 years, all his primary incisors showed chronic draining abscesses. The teeth were not carious and there was no history of trauma. Radiographs showed extremely large pulp chambers and poorly calcified dentine (Figure 5.5). Histologic studies of the extracted teeth revealed large quantities of interglobular dentine and extensions of pulp chambers into the incisal edges of the teeth (Figure 5.6).

The abscessed incisors were extracted soon after the initial examination. On subsequent visits, acid-etched composite resins were placed over the occlusal surfaces of the remaining primary teeth in an attempt to prevent further pulp exposures and abscesses. These resin caps were checked and adjusted regularly. However, in spite of this prophylactic procedure, all the remaining primary teeth subsequently became abscessed and required either extraction or endodontic treatment.



Fig 5.5. Periapical radiographs of the maxillary and mandibular anterior teeth of a male (Case 1) taken at initial examination. Note enlarged pulp chambers and periapical radiolucencies associated with the incisor teeth.



Fig 5.6. Section of a mandibular primary incisor from Case 1. Note the large size of pulp chamber, poorly calcified dentine (interglobular dentine) and extensions of the pulp chambers into the incisal edges of the teeth.

When the patient was seen by the author at 9 years of age, it was decided to use more aggressive methods to prevent abscesses in the permanent dentition. As soon as the first permanent molars erupted, the occlusal surfaces were capped with acid-etched composite resins. When the teeth erupted sufficiently, it was decided to cap them with stainless steel crowns. Because of the large pulp chambers (Fig 5.7) there was grave danger of pulp exposures if routine tooth preparation was undertaken. This problem was overcome by first placing separating elastics interproximally to open the contact areas between the teeth, (Seow, 1984b) thus reducing the need for proximal reduction. Occlusal reduction was achieved by reducing the occlusal composite resin caps placed earlier. By this method, the need to remove natural tooth substance is virtually eliminated and the possibility of pulp exposures reduced. Prior to cementation of the stainless steel crowns, any enamel not covered by the composite resin was lined with calcium hydroxide before cementation with zinc phosphate cement.

When the permanent incisors erupted, the decision as to whether to cap these teeth had to be made. As the maxillary and mandibular incisors were contacting only minimally, it was decided that wear on these teeth would be slight and the need for protection not great. However, the lower right lateral incisor subsequently became abscessed and endodontic therapy was instituted. This forced the author to review the decision not to cap

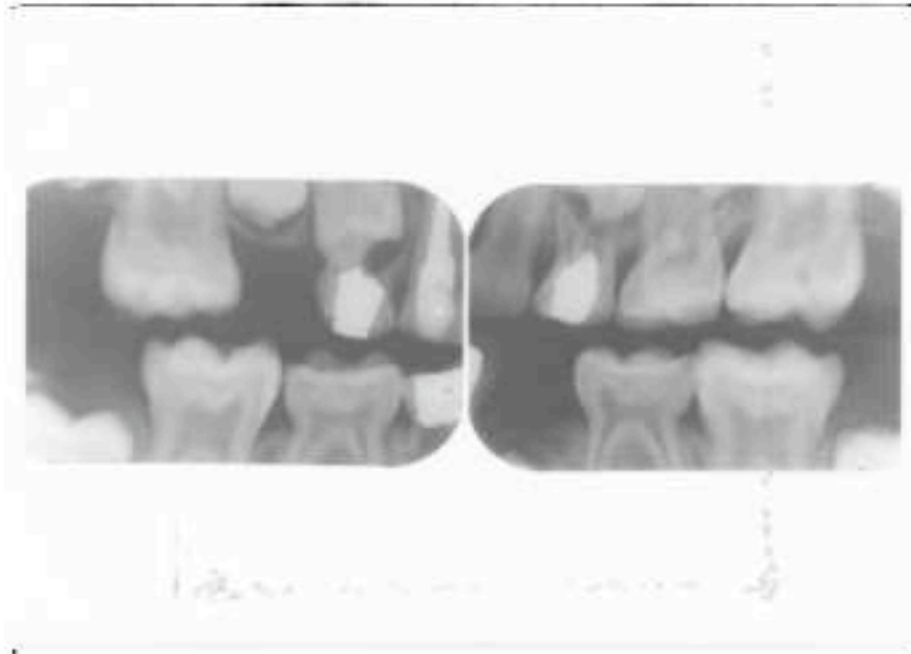


Fig 5.7. Bite-wing radiographs of Case 1 taken at age 10 years. Note Grade III severity of dental manifestations with enlarged pulp chambers and abnormally calcified dentine.

the incisors and on later visits, the incisal edges of these teeth were protected with acid-etched composite resins.

At the time of writing, the first premolars were in the early stages of eruption. A plan of treatment similar to that for the first permanent molars was suggested and acid-etched composite resins were used to cap the occlusal surfaces of the first premolars that emerged. Stainless steel crowns for these teeth were planned as soon as they have erupted into occlusion.

When the patient reaches adulthood, the stainless steel crowns should be replaced with full gold or porcelain bonded-to-gold crowns to increase fit and marginal adaptability.

DISCUSSION

This study of 13 patients with VDRR from several families illustrates the wide range of dental manifestations that are seen in this condition. These patients can be divided into 3 main grades according to the severity of dental signs: Grade I patients have minimal dental signs of the disease; Grade II patients usually show involvement of a few teeth only; and Grade III patients have severe dental manifestations such as multiple dental abscesses and grossly enlarged pulp chambers.

There are various factors which can account for the wide spectrum of dental manifestations in VDRR. First, genetic factors may play an important role in determining the severity of disease. It is apparent from this study that the severity of dental manifestations is similar within each family. For example, in 1 family (Cases 11-13), both the female patients and their affected mother showed only minimal dental signs of VDRR. In another family (Cases 5 and 10) both affected mother and daughter exhibited mild dental manifestations of the disease. It is likely that VDRR is inherited in several different forms varying in severity, with each affected family showing similar severity among its members.

Within each affected family, individual variations may arise. An important factor is the sex of the patient. Females tend to show less disease than males as expected of an X-linked trait. In females, partial protection is obtained from the presence of a normal X chromosome in addition to the X chromosome carrying the abnormal gene. Also, other factors such as hormones may influence the severity of disease in affected females. For example, it had been shown that there is no consistent correlation between the severity of hypophosphataemia and the severity of bone disease in females (Fraser & Scriver, 1976). The present study too, shows that dental signs are less severe in females. Out of 9 females, 7 can be classified into the group showing mild dental manifestations (Grade I), while the other 2 belonged to the group with moderate dental manifestations (Grade II). On the

other hand, the 2 children showing the most severe dental manifestations (Grade III) were both males (Cases 1 and 2). Another male patient (Case 3) showed moderate dental findings while the fourth male patient (Case 9) had no history of dental abscesses and no increased sizes of the pulp chambers. However, because the latter patient was only 5 years of age at the time of dental examination, it was difficult to determine the extent of involvement of the permanent teeth. Pliskin and colleagues (1975) reported a case of VDRR in whom only the permanent dentition showed obvious clinical manifestations.

Medical therapy received by the patients may influence the severity of dental manifestations. Oral supplementation of inorganic phosphate to replace the abnormal renal losses of phosphate is the usual method of treatment in VDRR. In addition, vitamin D in the form of calcitriol also is given to prevent phosphaturia and hypercalcaemia which may result from phosphate loading. In children with known family histories of the condition, diagnosis usually is made soon after birth. However, phosphate and vitamin D supplementation are not often given until at least after 9 months of age. This is because the low glomerular filtration rate in early infancy may prevent excessive losses of phosphate, thus reducing the need for early phosphate supplementation. In addition, constant monitoring of serum levels is vital in vitamin D supplementation and repeated blood sampling is not feasible in the very young infant.

Oral supplementary phosphate and calcitriol should improve dental calcification and prevent abscesses. However, because many patients are not diagnosed and treated until after 2 years of age, the entire primary dentition and permanent incisors and first molars do not receive the beneficial effects of medical therapy, and are at greatest risk for developing dental abscesses. In this series, the 2 patients (Cases 1 and 2) with the greatest number of abscesses were both diagnosed and treated only after 2 years of age; in both cases, the entire primary dentition became abscessed. In contrast, another male patient (Case 9) who was diagnosed and treated at a few months of age still has not developed any abscesses of the primary teeth and the pulps of his teeth appeared fairly normal on radiographs.

The results of this study (Table 5.1) indicate that with the exception of a mildly affected female (Case 10) who was not diagnosed until 28 years of age, the earlier the institution of medical therapy, the less severe the dental manifestations. Further longitudinal clinical as well as histological studies on teeth need to be performed to establish the importance of medical therapy on dental calcification in VDRR.

Prevention of dental abscesses is an important aim in dental management of VDRR. Even minimal wear of the teeth can result in pulp exposures and protection of functional tooth surfaces should be considered. The need for such prophylactic coverage varies with the severity of dental manifestations.

Besides prophylactic coverage to prevent occlusal wear, routine preventive care for dental caries is extremely important as minimal caries can lead to pulp exposures. Fluoride therapy, dietary advice, and oral hygiene therapy should be given regularly.

Besides prophylactic treatment, control of existing infection is important in the dental management of the patient with VDRR. Most clinical studies report success with routine endodontic procedures for abscessed teeth in VDRR. However, the thin and poorly calcified dentine walls of the root canals do not allow excessive instrumentation and care has to be taken to prevent perforation and root fracture. Also, if abscessed primary teeth are extracted, considerations must be given to space maintenance.

CHAPTER SIX

**MICROMORPHOLOGIC FEATURES OF DENTINE IN VITAMIN D-RESISTANT
RICKETS: CORRELATION WITH CLINICAL GRADING OF SEVERITY**

INTRODUCTION

Vitamin D resistant rickets (VDRR), also known as familial hypophosphataemia is the most common form of rickets in developed countries today (Fraser and Sriver, 1976). The disease which is inherited in an X-linked dominant manner results from a selective disorder of transepithelial transport of phosphate, leading to decreased tubular reabsorption of phosphate and persistent hypophosphataemia (Harrison and Harrison, 1964).

VDRR is of special significance to paediatric dentists because of the characteristic multiple "spontaneous" dental abscesses which are often associated with the disease (Harris and Sullivan, 1960; Seow, 1984a; Herbert, 1986). In fact, many patients with VDRR were first diagnosed by dentists from these dental features as the general signs and symptoms of rickets are usually not obvious until the patients are over 18 months of age. The dental abscesses are due to defective dental mineralization which predisposes to early pulp exposures from minimal caries or attrition.

In VDRR the abnormal dental mineralization is characteristically observed in dentine where large amounts of poorly mineralized globular dentine and tubular defects extending close to the amelodentinal junction are observed (Soni and Marks, 1967; Sauk and Witkop, 1973). Enamel hypoplasia occurring concurrently with these defects have also been reported (Marks et al, 1965;

Soni and Marks, 1967; Tulloch and Andrews, 1983; Seow and Latham, 1986).

In a previous study of 13 patients affected by VDDR, Seow and Latham (1986) reported that the dental findings occurred in a spectrum of manifestations ranging from minimal to severe. Based on the history of dental abscesses and the radiographic appearances of the teeth, 3 grades of oral manifestations were proposed by the authors, viz Grade I: minimal or no dental manifestations; Grade II: moderate pulp enlargement with a few teeth abscessed; Grade III: extremely large pulp chambers and multiple dental abscesses.

In the present study, the author examined teeth from patients with different clinical grades of VDDR to determine if these clinical grades could be correlated with histological findings. In addition, microscopic findings were analysed in relation to genetic data and medical treatment to gain further insight into the pathogenesis of the dental defects in VDDR.

PATIENT AND METHODS

Patients

Naturally exfoliated and extracted primary teeth were collected from 5 patients with an established diagnosis of VDDR. These patients formed part of the study population reported in a previous investigation (Seow and Latham, 1986). Teeth were not

available from the remaining patients in the previous study. Details of medical histories and treatment were obtained from the patients as well as from hospital charts. There were 2 females and 3 males and their ages at the time of study ranged from 7 to 15 years. The ages of diagnosis and the start of medical treatment in these children varied from 9 months to 4 years 6 months of age. At the time of study, all patients were on phosphate replacement therapy and calcitriol.

The response to medical treatment was assessed periodically using standard biochemical, radiological and clinical criteria. All patients were reported to be well controlled with acceptable growth rates and minimal biochemical and radiological evidence of rickets.

As described in the previous study (Seow and Latham, 1986), two patients had been diagnosed as having minimal dental manifestations of VDRR, i.e. Grade I severity, and another two had severe dental signs, i.e. Grade III activity. The fifth patient had been classified as showing Grade II severity with moderate dental findings.

Four primary teeth were obtained from each of the five patients for histologic analysis.

Histologic Sections

The teeth were embedded in plastic and sectioned sagittally to 100 μ m using a Bovis Planometer sectioning machine.

Hand polishing further reduced the section to 80 μ m. The undecalcified sections were mounted on glass slides and studied under transmitted and polarizing light microscopy at various magnifications. Photographs were taken using a Leitz Ortholux microscope coupled with a Wild Photoautomat exposure control unit and camera.

RESULTS

The general histological features of VDRR were noted in all the sections. Deficient mineralization of dentine, manifested as globular dentine with varying degrees of interglobular spaces was observed in all the teeth. The relative amount of globular dentine varied in teeth from different patients, and was also observed in the roots of the teeth.

The enamel, amelodentinal junctions and cementum appeared normal.

Establishment of 3 Histological Grades

The sections were first analysed with regard to the amount of globular dentine present, as well as its density. Using these

criteria, a histological grading was established as follows (Table 6.1). In Grade I the amount of globular dentine was less than 50% of the total dentine thickness. In addition, the interglobular spaces were small, indicating that the defect in dentine mineralization was mild. Figure 6.1 shows a representative tooth affected by Grade I severity, and Figure 6.2 depicts an area of affected dentine under higher magnification (x400), showing the small amount of globular dentine formation and the minimal interglobular spaces present.

In Grade II severity, the amount of globular dentine constituted greater than half of the total dentine thickness but did not involve its entire thickness, and the interglobular spaces appeared moderately large. Figure 6.3 shows a typical section affected by Grade II severity and Figure 6.4 depicts an area of affected dentine under higher magnification (x400) showing moderate amount of globular dentine and interglobular spacing.

Grade III is the most severely affected grade, with globular dentine formation extending almost throughout the entire dentine thickness and the interglobular spaces large. In addition, in Grade III sections there was a greater tendency for the occurrence of dentinal clefts which may extend from the pulp to the DEJ. These histological features are exemplified in Figure 6.5. In addition, Figure 6.6 shows an area of affected dentine under higher magnification (x400), depicting the severity of globular dentine formation and the large interglobular spaces. For

Table 6.1. Appearance of dentine in the 3 histological grades of vitamin D-resistant rickets.

Histologic Grade	Appearance of dentine	
	Amount of globular dentine	Interglobular spaces
I	<50% of total dentine thickness	Minimal
II	>50% but does not involve entire dentine thickness	Moderate
III	Almost entire thickness of dentine involved	Large

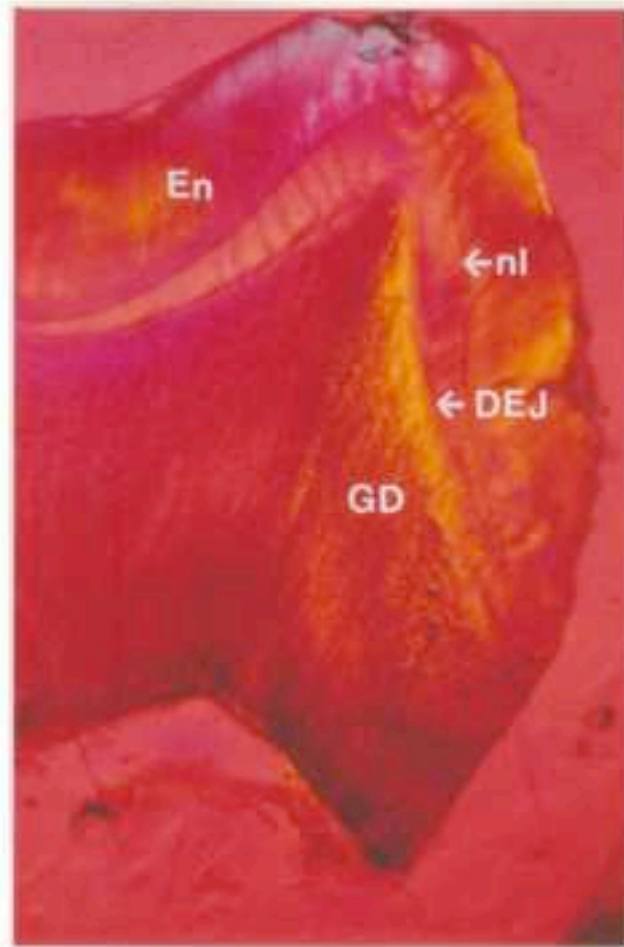


Fig. 6.1 Ground section of a mandibular primary first molar tooth affected by Grade I severity (Original mag. x40). Note the minimal amount of globular dentine formation and the small interglobular spaces. The neonatal line clearly evident in enamel and that in dentine may be extrapolated from this line. Thus, it may be observed that the prenatally-formed dentine is fairly normal.

nl: neonatal line; DEJ: dentinoenamel junction; GD: globular dentine; En: enamel.

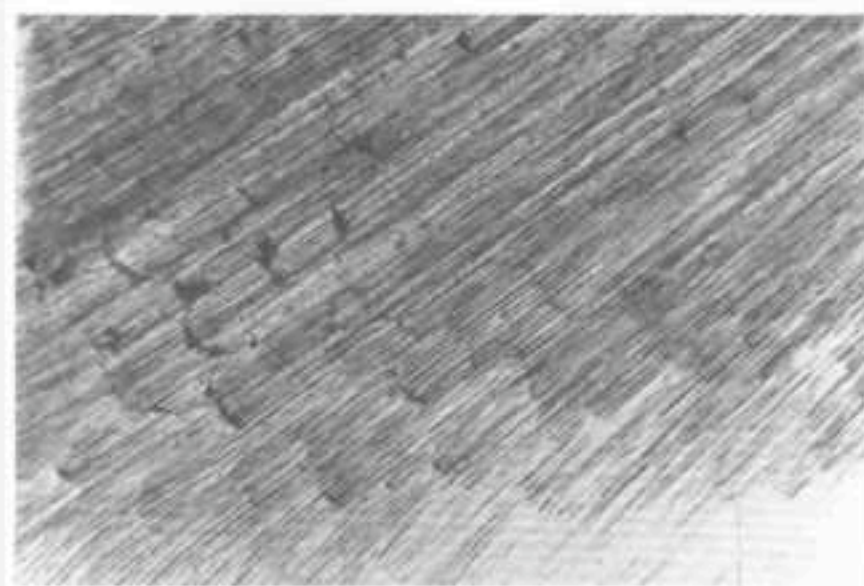


Fig. 6.2 Higher magnification (Original mag. $\times 400$) of the dentine in the section shown in Fig. 6.1 (Grade I severity) showing minimal amount of globular dentine. For comparison purposes, Figs. 6.2, 6.4 & 6.6 were taken from approximately the same location of each tooth (directly beneath the cusp tips) and at the same magnification.



Fig. 6.3 Ground section of a maxillary primary molar tooth affected by Grade II severity (Original mag. x40). Note the moderate amount of globular dentine formation, and the moderately large interglobular spaces.

nl: neonatal line; DEJ: dentinoenamel junction; GD: globular dentine; En: enamel; PD: prenatally-formed dentine.

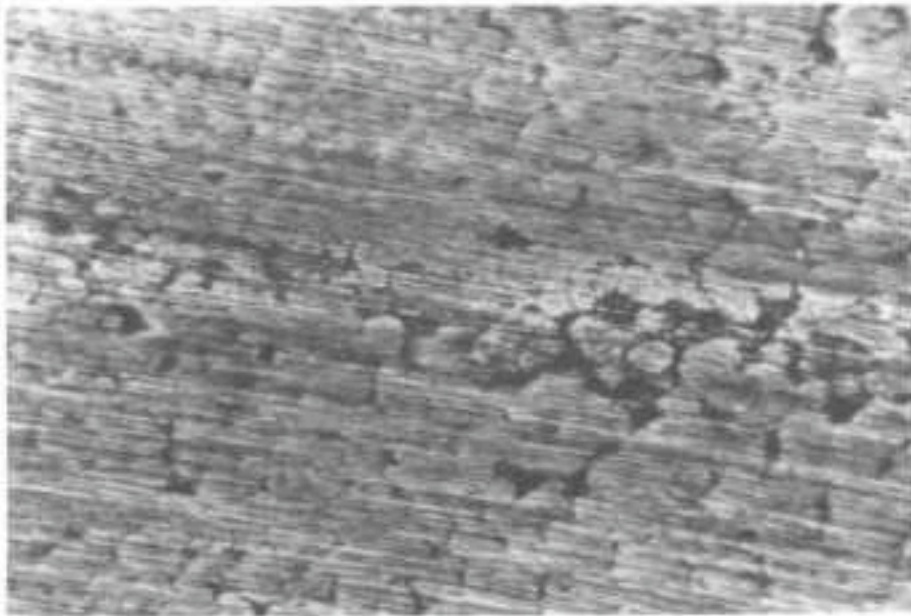


Fig. 6.4 Higher magnification (Original mag. x400) of the dentine in the section depicted in Fig. 6.3 (Grade II severity) showing moderate amount of globular dentine formation.



Fig. 6.5 Ground section of a mandibular primary canine tooth affected by Grade III severity (Original mag. $\times 40$). Note that globular dentine is present from the dentino-enamel junction to close to the pulpal surface. The interglobular spaces are also large and clefts in dentine are observed.

En: enamel; DEJ: dentinoenamel junction; PD: prenatally formed dentine; GD: globular dentine.

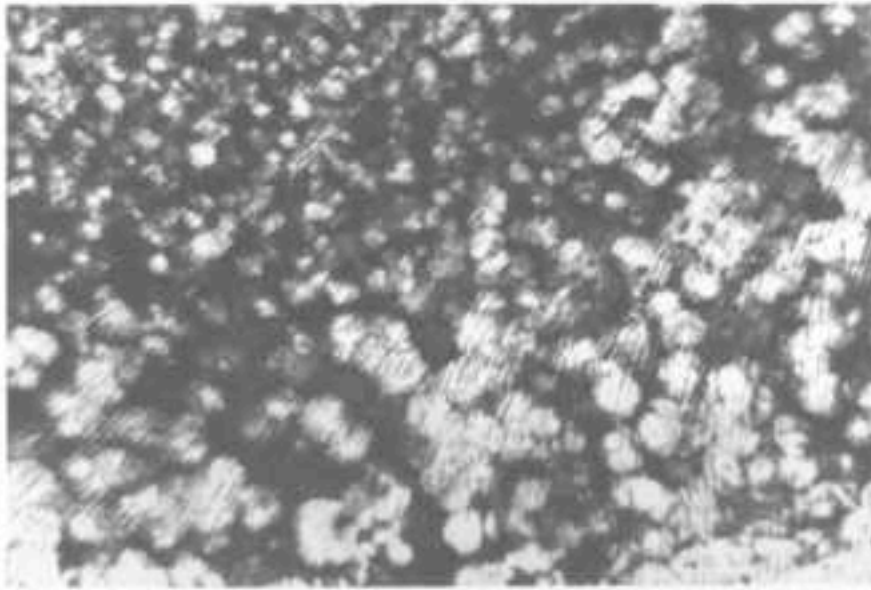


Fig. 6.6 Higher magnification (Original mag. x400) of the dentine in the section shown in Fig.6.5 (Grade III severity) depicting large interglobular spaces and severe globular dentine formation.

comparative purposes, Figures 6.2, 6.4 and 6.6 were taken from the area of globular dentine immediately beneath the cusp tips of the teeth shown in Figures 6.1, 6.3 and 6.5 respectively.

Correlation of Histologic and Clinical Gradings

The histologic sections of all the teeth were first grouped according to the above criteria into the 3 histological grades without any reference to the clinical gradings previously given to the patients. The histological gradings of all the teeth from each patient were noted. It was observed that for each patient, the histological grading was similar in all of the teeth examined. These histological gradings were then correlated with the clinical gradings of the patients which had been given previously, based on the number of dental abscesses and the sizes of pulp chambers (Seow and Latham, 1986).

The results, as shown in Table 6.2, clearly indicate that there is a consistent correlation of clinical and histologic gradings in all the patients studied.

Appearance of Prenatally-Formed Dentine

In the primary dentition, it is possible to distinguish the regions of the teeth mineralized before and after birth by locating the neonatal line in histological sections. Although the neonatal line is not often clearly discernible in dentine, it may be extrapolated from that in enamel, being considered to be of equidistance and of the similar angular inclination from the

Table 6.2. Dental manifestations of VDRR: Correlation of clinical and histological gradings.

Patient (age)	No. of Abscessed Teeth	Pulp Enlargement	Clinical Grading	Histologic* Grading
M.G. (12 yrs)	21	+++	III	III
S.S. (9 yrs)	20	+++	III	III
N.S. (15 yrs)	3	+	II	II
K.B. (11 yrs)	0	-	I	I
M.B. (7 yrs)	0	-	I	I

* Four deciduous teeth from each patient were used for histologic analysis. The histologic grading of all teeth from any individual patient was identical in all cases.

dentinoenamel junction (Massler et al, 1941; Osborn and Ten Cate, 1983).

Using this technique, the prenatally-formed dentine was located in all the teeth from each patient. The results (Table 6.3) showed that in one patient (SS) prenatally-formed globular dentine was present, indicating that the defective mineralization occurred in-utero. Of great significance is that in this male patient, the affected mother was not treated during pregnancy. Thus, it is most likely that hypophosphataemia in the mother had affected in-utero mineralization of the primary teeth. This prenatally-formed globular dentine is evident in Figure 6.5. Figure 6.7 shows this area under higher magnification (x100). Of further interest is the observation that although this area of dentine is also globular, the interglobular spaces are markedly smaller, indicating a better degree of mineralization.

In contrast, in the other 4 patients, the prenatally-formed dentine appeared fairly normal, and formation of globular dentine appeared to have commenced only after birth. It is of significance that in all these patients, the affected mothers had phosphate replacement therapy during pregnancy, suggesting that correction of hypophosphataemia in the mother might prevent defective in-utero calcification of the primary dentition of the fetus. Figure 6.3 clearly depicts the apparently normal prenatally-formed dentine and Figure 6.8 shows this area under higher magnification (x100).

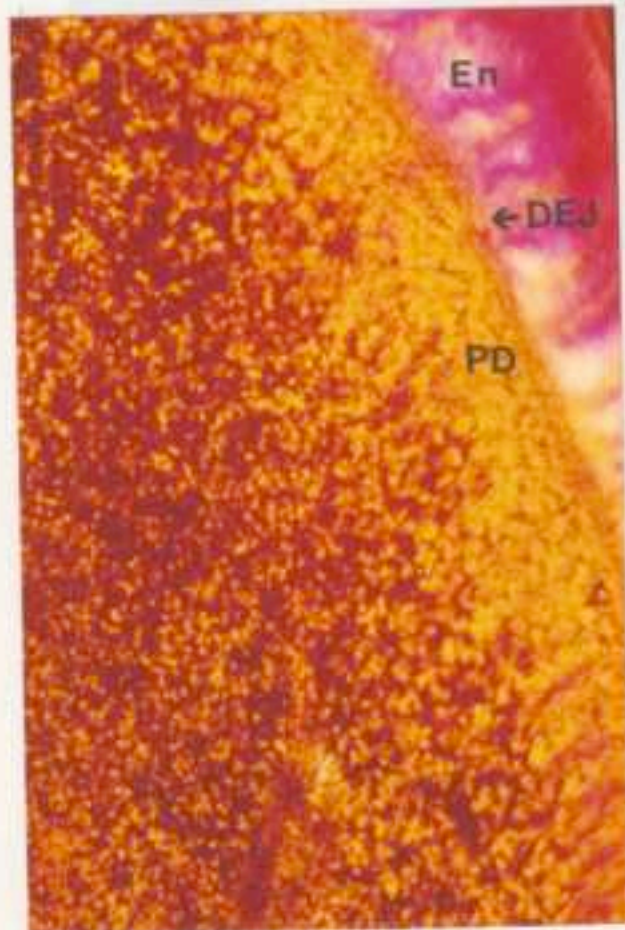


Fig. 6.7 Higher magnification (Original mag. x100) of the prenatally-formed dentine in the section depicted in Fig. 6.5. Note that although the band of dentine closest to the DEJ is better calcified than the later-formed dentine, it is still globular in appearance.

En: Enamel; DEJ: Dentinoenamel junction; PD: Prenatally-formed dentine.



Fig. 6.8 Higher magnification (Original mag. x100) of the prenatally-formed dentine in the section depicted in Fig. 6.3. Note the normal appearance of the band of dentine formed prenatally, in sharp contrast to that seen in Fig. 6.7.

nl: neonatal line; DEJ: Dentinoenamel junction; PD: prenatally-formed dentine; En: enamel.

Table 6.3. Appearance of prenatally-formed dentine in patients with VDRR.

Patient	Sex	Mother affected	Mother treated during pregnancy	Prenatally formed interglobular dentine ⁺
M.G.	M	No*	—	0
S.S.	M	Yes	No	+++
N.S.	F	Yes	Yes	0
K.B.	F	Yes	Yes	0
M.B.	M	Yes	Yes	0

⁺ For each patient, 4 primary teeth were sectioned. The prenatally formed parts of each tooth were first identified using the neonatal line as indicator. In all cases results were similar in all teeth.

* This case of an affected male child with an unaffected mother in an X-linked dominant disease may indicate a new mutation.

Appearance of Mantle Dentine

It was a consistent observation that the mantle dentine always appeared to be better mineralized compared to the later-formed dentine. This interesting finding, seen in both coronal and radicular dentine, was present even in the Grade III sections showing severe globular dentine formation (Patient SS, Table 6.3). In these sections although the mantle dentine was also globular, it appeared better mineralized than the dentine formed later.

DISCUSSION

Although enlarged pulp chambers and globular dentine have been associated with VDRR for some time (Harris and Sullivan, 1960; Marks et al, 1965; Archard and Witkop, 1966; Pliskin et al, 1975; Gardner et al, 1969; Vasilakis et al, 1980; Cohen and Becker, 1976; Soni and Marks, 1967; Gallo and Merle, 1979), there have been few detailed histological studies of the teeth in this condition. Variability in the amount of globular dentine formation among affected patients was first noted by Soni and Marks (1967) as an incidental finding in their studies. Later Tracy et al (1971) subjectively graded severity of globular dentine formation from unaffected to severe in their histological investigation of teeth from 7 patients with VDRR, but no relationship of the histological findings to dental clinical data was mentioned.

The present investigation extends the earlier observations that there is a spectrum of severity from Grades I to III of globular dentine formation in teeth affected by VDRR and that this histological spectrum correlates closely with the clinical spectrum previously reported (Seow and Latham, 1986). This correlation is not surprising as the teeth most severely affected by globular dentine formation are also those most prone to the development of dental abscesses.

Of even greater significance is the finding from this study that the presence of prenatally-formed globular dentine may be related to an affected but not medically treated mother. In contrast, patients with affected mothers who took phosphate supplements in pregnancy showed prenatally-formed dentine which appeared normal. This may indicate that in affected females carrying affected children, the fetus is unable to obtain sufficient phosphate for normal mineralization of dentine in-utero. However, if the mother is supplemented with phosphate, globular dentine formation may be prevented in the fetus.

To substantiate this hypothesis, it was shown in the present study, that one patient (MG, Table 6.3) who had an unaffected mother, showed normal prenatally-formed dentine, in sharp contrast to the severe (Grade III) globular dentine formed post-natally. In this case, extensive tests in the mother had definitively established that she did not have VDRR, and the disease in her son was probably caused by a new gene mutation.

This unusual case may indicate that a normal mother protects her affected children from globular dentine formation in-utero. Further supportive evidence may be obtained from histologic analysis of teeth from affected female children born to unaffected mothers; however, this awaits further investigations.

On the basis of the above findings, implications for genetic diagnosis may be suggested. In cases of disputed or unknown family histories, it may be possible to determine whether the mother is affected by examining the presence of globular dentine in the prenatally-formed regions of the child's teeth.

The reasons for the broad spectrum of clinical and histological manifestations of VDRR are unclear and may be related to several factors. Firstly, it is possible that VDRR may be inherited in a wide spectrum of severity. Secondly, females tend to get less severe disease, being protected by the presence of an additional X-chromosome which is normal (Avioli et al, 1967; Sauk and Witkop, 1973). Thirdly, medical therapy with phosphate supplementation and calcitriol (vitamin D₃) may improve dental mineralization. In the present study, the two patients with Grade III severity dental manifestations were both diagnosed and treated after the age of two years, when most of the primary dentition is already mineralized.

The value of a grading system in dental conditions is that it provides some guidelines as to the clinical management of the

patients (Seow and Latham, 1986). In VDRR, prevention of dental abscesses plays a central role in management. Patients exhibiting Grades II and III severity should be placed on an aggressive preventive regime which includes prophylactic stainless steel crowns for posterior teeth (Seow, 1984a, 1984b; Seow & Latham, 1986) and adhesive resins for anterior teeth. However, patients with Grade I severity may require only routine preventive measures such as fissure sealants and topical fluoride therapy.

In conclusion, the present histological study has substantiated the findings of the previous clinical study by Seow and Latham (1986) that there is a spectrum of dental manifestations in VDRR. In addition, it was established that adequate phosphate supplementation in a hypophosphataemic mother might prevent the formation of globular dentine in the fetus in-utero.

CHAPTER SEVEN

**A CONTROLLED STUDY OF THE ASSOCIATION OF
VARIOUS DENTAL ANOMALIES WITH HYPODONTIA**

INTRODUCTION

Hypodontia or agenesis of a few permanent teeth is one of the most common dental anomalies in man although it is rare in other mammalian species. The prevalence of hypodontia in the permanent dentition has been reported from 2.8 percent (Byrd, 1943) to 10.2 percent (Ferguson, 1973). Racial variation in prevalence is well documented and suggests strong genetic influence in its aetiology.

The most commonly missing tooth is unequivocally the third molar which shows a prevalence of hypodontia of 1 percent in African Negroes to 30 percent in Japanese populations (Stewart et al, 1982). The next most commonly missing tooth is usually reported to be the mandibular second premolar, followed by the maxillary lateral incisor, although many studies report the maxillary second premolar as the third most commonly missing tooth (Silverman and Ackerman, 1979).

It is now well known that reduction in tooth size is associated with agenesis of the teeth, with many family and twin studies indicating that this defect is an expression of the same disorder (Garn et al, 1963). In addition, ankylosis of primary molars ~~have~~ also been associated with hypodontia of corresponding premolars (Brown, 1981; Brearley & McKibben, 1973). However, these two anomalies have been studied in association with hypodontia in isolation only. It is likely other genetic and

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environmental influences may also be associated with agenesis of the teeth, but these have not been well investigated. The present study examines the association of various dental anomalies in a group of children with hypodontia compared with a control group without the condition.

PATIENTS AND METHODS

Patient records

Panoramic radiographs and clinical records were the source of data in this study. Current patient records kept at the Paediatric Dentistry Unit of the Dental School, University of Queensland were screened to obtain 1032 records with panoramic radiographs for analysis. There ~~were~~ ^{was} a total of 529 males and 503 females. The mean age at the time of radiography was 11 yrs 1 mo \pm 2 yrs 11 mo (range 6-19 years). All the patients were Caucasian and did not suffer dysmorphic medical syndromes. Past dental histories were checked to ensure that extractions of permanent teeth were not diagnosed as congenital absence.

was

Diagnostic criteria

Hypodontia was diagnosed from both clinical and radiographic criteria. The numbers and types of teeth missing were noted. Third molars were excluded in the consideration of hypodontia in this study of young subjects.

Taurodontism was evaluated by measuring the crown (C), body (B) as well as the root length (R) of the mandibular first permanent molar from the panoramic radiograph as described in an associated study (Seow & Lai, 1989). It was established in the study that such measurements of the mandibular first molar did not differ significantly from those taken from a long-cone periapical radiograph. Taurodontism was diagnosed if the crown-body to root length (CB:R) ratio was greater than 1:1 (Seow & Lai, 1989).

Ankylosis was diagnosed if a tooth showed infraocclusion (Brown, 1981), i.e. at least 1 mm below the occlusal plane. In all cases, this was clearly evident from the panoramic radiograph alone.

Enamel hypoplasia was diagnosed if at least one tooth showed a break in the continuity or surface loss of enamel. This was ascertained from clinical records and confirmed with radiographs whenever possible.

Other dental anomalies such as fusion, gemination, dilaceration of roots and impacted teeth were also diagnosed from clinical and radiographic criteria.

Hypodontia patients

Of the total number of patients selected, 66 (6.4%) had agenesis of at least one tooth. In this group, there were 36

males and 30 females and their mean age at the time of radiography was 11 yrs 1 mo \pm 2 yrs 8 mo (range 6-19 years). All these patients showed hypodontia as an isolated trait and did not suffer these defects as part of an overall syndrome.

Control patients

A control patient who matched the study case for sex as well as the age at radiography, was selected for every case of hypodontia (36 males and 30 females). Their mean age at the time of radiography was 11 yrs 6 mo \pm 2 yrs 11 mo (range 6-19 years). All control patients were also Caucasian and were shown to have radiographic evidence of complete permanent dentitions which may or may not be erupted.

Statistical analysis

The student's t-test, Chi-square test, as well as Fisher's exact test, as appropriate, were used for statistical analysis of the data.

RESULTS

Features of hypodontia

i) Frequency of type of tooth missing

The frequency of each type of tooth missing was first analysed. The results are shown in Figure 7.1. The mandibular second premolar was the most commonly missing tooth, constituting 19.4 percent of all the missing teeth (61 out of 314 missing

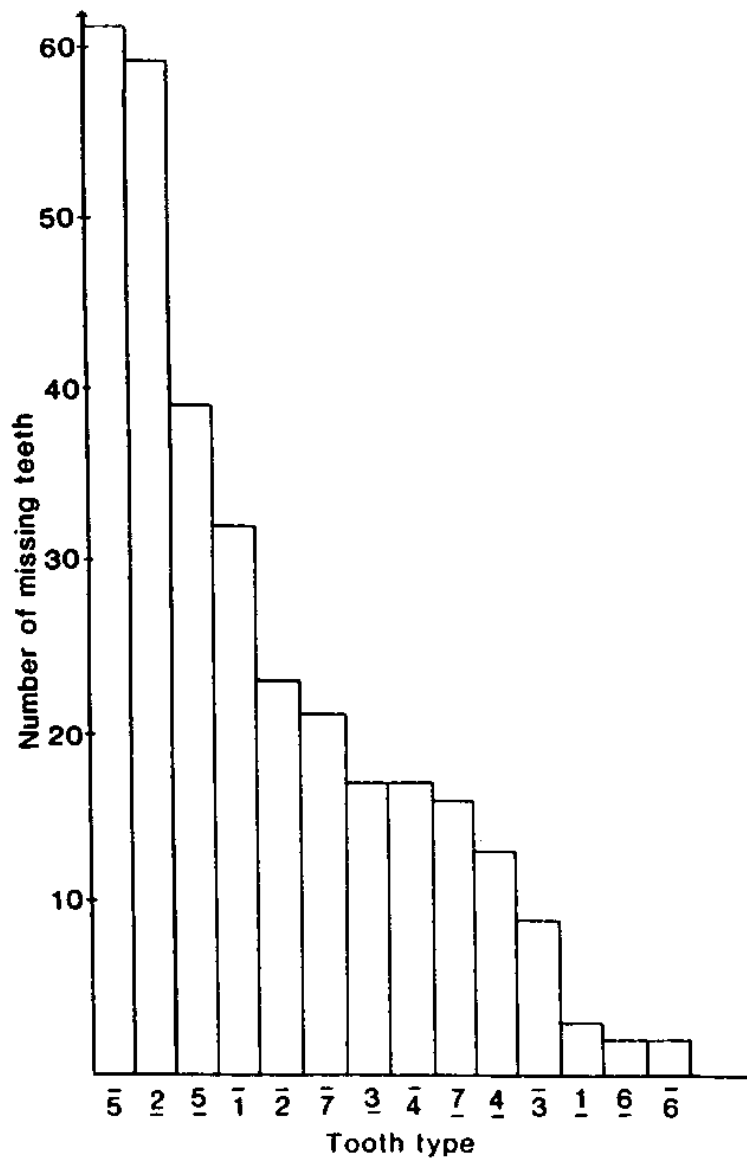


Figure 7.1 Frequency of each type of missing tooth

teeth). Only slightly lower in frequency was the maxillary lateral incisor, which formed 18.8 percent. The third most commonly missing tooth was the maxillary second premolar (12.4%), followed by the mandibular central incisor (10.2%). The other missing teeth in decreasing order of frequency include the mandibular lateral incisor (7.3%), mandibular second molar (6.7%), mandibular first premolar and maxillary canine (5.4%), maxillary second molar (5.1%), maxillary first premolar (4.1%), mandibular canine (2.9%) and lastly, the maxillary central incisor, maxillary first molar and mandibular first molar (1.0% each).

ii) Number of missing teeth

The mean number of missing teeth found in the hypodontia group of patients was 4.72 ± 3.04 . As shown in Table 7.1, more than half of these patients were missing up to 3 teeth and the remainder from 4 to more than 6 teeth per subject.

iii) Sex differences

The prevalence of hypodontia was also analysed according to sex. The results (Table 7.2) showed that there were no significant differences between the sexes, with 7.0 percent of males showing hypodontia compared to 5.8 percent of females ($p > 0.1$). In addition, the females did not show a greater tendency for more teeth to be missing than males (Table 7.1).

Table 7.1. Number of missing teeth in patients with hypodontia.

Number of missing permanent teeth	No. of patients		
	Male	Female	Both Sexes (%)
1	5	8	13 (20%)
2	10	9	19 (29%)
3	2	3	5 (8%)
4	6	2	8 (12%)
5	2	2	4 (6%)
6	4	2	6 (9%)
More than 6*	7	4	11 (17%)
Total	36	30	66 (100%)

The difference in the mean number of missing teeth in females and males is not significant, $p > 0.1$

* Maximum number of missing teeth is 22

Table 7.2. Prevalence of hypodontia according to sex

No. of patients with hypodontia	
Females (n=503)	29 (5.8%)
Males (n=529)	37 (7.0%)
Total (n=1032)	66 (6.4%)

The difference in prevalence of hypodontia between the sexes is non-significant.

iv) Frequency of unilateral and bilateral hypodontia

In the patients with hypodontia, the frequency of unilateral and bilateral hypodontia were determined, and the results shown in Table 7.3. In nearly all the tooth types analysed, the frequency of bilaterally missing teeth greatly exceeded that of unilaterally missing teeth. Overall, 74.2 percent of all cases showed bilaterally missing teeth.

Association of various dental anomalies with hypodontia

Clinical and radiographic records of hypodontia patients and controls were analysed for the presence of other dental anomalies. The results are shown in Table 7.4. Ankylosis of primary molars was strongly associated with hypodontia, being observed in 65.7 percent of all hypodontia patients compared to only 1.5 percent in control patients ($p < 0.001$).

Taurodontism was also more commonly observed in the hypodontia group compared to control (34.3% vs. 7.1%, $p < 0.001$). In addition, conical (reduced) maxillary lateral incisors were observed in 8.9 percent of the hypodontia group whereas there was no patient with this trait in the control group. This difference is statistically significant ($p = 0.03$). Enamel hypoplasia of at least one tooth also appeared significantly more common in the hypodontia group compared to the controls (11.9% vs. 0%, $p = 0.003$).

Table 7.3. Frequency of unilateral and bilateral hypodontia.

	Number of Patients		
	Unilateral	Bilateral	Total
<u>Maxillary teeth</u>			
Central incisor	1	1	2
Lateral incisor	11	24	35
Canine	1	8	9
First premolar	3	5	8
Second premolar	5	17	22
First molar	0	1	1
Second molar	0	8	8
<u>Mandibular teeth</u>			
Central incisor	2	15	17
Lateral incisor	5	9	14
Canine	1	4	5
First premolar	5	6	11
Second premolar	11	25	36
First molar	0	1	1
Second molar	1	10	11
Total	46	134	180
Percentage	25.6%	74.4%	100%

The difference in frequency between unilateral and bilateral hypodontia is statistically significant, $\chi^2 = 12.1$, $df = 1$, $p < 0.001$.

Table 7.4. Association of various dental anomalies with hypodontia

Associated dental anomaly	No. of Patients Affected (percentage)		p value
	Hypodontia Group (n=66)	Control Group (n=66)	
Ankylosis of primary molars	44 (65.7%)	1 (1.5%)	<0.001
Taurodontism	23 (34.3%)	5 (7.1%)	<0.001
Conical incisors	6 (8.9%)	0	0.03
Enamel hypoplasia	8 (11.9%)	0	0.003
Fusion of teeth	1 (1.5%)	0	1.00
Gemination of teeth	1 (1.5%)	0	1.00
Root dilaceration	1 (1.5%)	4 (5.7%)	0.37
Impacted teeth	0	6 (8.9%)	0.03

The Fisher's exact test was used to determine p values.

In contrast, in the control group, impacted teeth (mandibular and maxillary canines and premolars) were observed in 6 patients (8.9%) whereas there was no such case in the hypodontia group. This difference is statistically significant ($p=0.03$).

Other dental anomalies such as fusion and gemination as well as root dilaceration were considered, but no statistical differences between the groups were found.

Dental anomalies associated with different types of hypodontia

It is of interest to determine the type of hypodontia observed in association with those anomalies previously determined to be significant. The results are shown in Table 7.5. Ankylosis, taurodontism and enamel hypoplasia are most commonly observed in cases of multiple missing teeth which are responsible for 52.3 percent of all cases of ankylosis, 51.9 percent of taurodontism and 75.0 percent of all cases of enamel hypoplasia.

In contrast, half of all cases of conical (reduced) incisors are observed in patients with missing premolars, and only 16.7 percent in patients with multiple missing teeth.

DISCUSSION

The present study of Caucasian patients confirms and extends some of the previous observations on hypodontia. Excluding third

Table 7.5. Dental anomalies associated with different types of hypodontia.

No. of patients with missing teeth (percentage) (n=66)					
Associated Dental Anomaly	Central incisors only	Lateral incisors only	Premolars only	Multiple Missing Teeth	Total
Ankylosis of primary molars	1 (2.3%)	8 (18.2%)	12 (27.3%)	23 (52.3%)	44
Taurodontism	0	3 (11.1%)	10 (37.0%)	14 (51.9%)	27
Conical incisors	0	2 (33.3%)	3 (50.0%)	1 (16.7%)	6
Enamel hypoplasia	1 (14.3%)	0	1 (14.3%)	6 (75.0%)	8

molars, a prevalence of hypodontia of permanent teeth of 6.4 percent was noted, which is well within the range of 2.8 percent (Byrd, 1943) and 10.2 percent (Ferguson et al, 1973) that had been reported previously. This suggests that although the subjects in this study were obtained from a treatment centre there is probably minimal bias on patient selection.

It was also shown in this study that the mandibular second premolar was the most commonly missing tooth, confirming the results of previous investigators (Byrd, 1943; Clayton, 1956; Grahnen, 1956; Glenn, 1961; Castaldi, 1966; Blayney & Hill, 1967; McKibben & Brearley, 1971; Hundstadbraten, 1973; Silverman & Ackerman, 1979). In addition, we have shown that the second most frequently missing tooth was the maxillary lateral incisor, supporting the results of Grahnen (1956), Glenn (1964) as well as Silverman and Ackerman (1979). However, other investigators have observed that the maxillary second premolar is the second most frequently missing tooth (Gimnes, 1964; Castaldi, 1966; Hundstadbraten, 1973), indicating that these results are equivocal.

An important finding of this study is that hypodontia is associated with several other anomalies of the dentition. Ankylosis or submergence of primary teeth was the most frequent dental anomaly associated with missing teeth, being present in over 65 percent of the hypodontia patients. Although this finding has been observed by previous investigators studying

ankylosis of teeth (Brown, 1981; Steigman et al, 1973), the possible reasons for the association of the two anomalies have not been established. It may be postulated that both environmental and genetic factors are involved. As all the ankylosed primary teeth were associated with agenesis of corresponding premolars it is likely that the absence of premolars may alter the delicate physiological balance of root resorption and repair in the primary molar, resulting in ankylosis of the tooth. Alternatively, it is also possible that both hypodontia and ankylosis may be inherited as associated traits (Roberts, 1973; Steigman et al, 1973).

Taurodontism, which describes a tendency for the body of a tooth to enlarge at the expense of the roots (Jaspers, 1981), has been previously noted in syndromes with malformation of multiple systems which also demonstrate oligodontia. These include the tricho-dento-osseous (TDO) syndrome (Lichtenstein et al, 1972), Klinefelter syndrome (Stewart, 1974), otodontodental dysplasia (Levin et al, 1975), ectodermal dysplasia (Stenvik et al, 1972), Down syndrome (Jaspers, 1981) and Nance-Horan syndrome (Seow et al, 1985a). In contrast, the present study shows that taurodontism may also be seen in patients with hypodontia uncomplicated by systemic involvement.

The finding that there is a significant association between enamel hypoplasia and hypodontia not involving systemic syndromes has not been noted previously. It may indicate a common origin

for both dental anomalies, most likely an aberration of ectodermal derivatives (Barjian, 1960). However, it is also possible that a single or concurrent environmental factor may have been responsible for the aetiology of both defects. For example, previous authors have noted that local infection as well as radiation may cause both hypodontia and enamel hypoplasia (Werther & Rothenberg, 1939; McCormack and Filostrat, 1967; Weyman, 1968).

The association of reduced incisors with agenesis of other teeth has already been well documented (Baum & Cohen, 1971; Alvesalo & Portin, 1969; Keene, 1971; Sofaer et al, 1971). However, genetic implications of this in the inheritance of hypodontia are currently under debate. Some researchers have suggested that hypodontia is caused by a single gene with pleiotropic manifestations which controls the size of individual teeth. Hence conical incisors are believed to be reduced forms of the hypodontic trait. In contrast, other workers (Rose, 1966; Baum & Cohen, 1971) have indicated that hypodontia is likely to be controlled by a polygenic system. Various statistical analyses using single locus and polygenic models have demonstrated this possibility (Suarez & Spence, 1974; Grahnen, 1956).

In conclusion, the present study has found significant association of hypodontia with ankylosis of primary molars, taurodontism, enamel hypoplasia and conical (reduced) incisors. While it has been established without doubt from numerous family

studies that hypodontia is an inherited trait, the aetiologies of associated dental anomalies are more difficult to determine. Nevertheless in all patients with hypodontia the clinician should be alerted to the possibility of these associated anomalies and their accompanying clinical problems.

CHAPTER EIGHT

ASSOCIATION OF TAURODONTISM WITH HYPODONTIA: A CONTROLLED STUDY

INTRODUCTION

The term taurodontism was first used by Keith in 1913 to describe the molars of Neanderthal human fossils which "had a tendency for the body of the tooth to enlarge at the expense of the roots". This trait which is of significance to dental clinicians is also of interest to anthropologists in the determination of the evolution of man (Shaw, 1928; Jorgensen, 1982).

Taurodontism has been reported as an isolated trait in many case reports (Lunt, 1954; Album, 1958; Mangion, 1962; Hamner et al, 1964; Metro, 1965; Regattieri and Llewellyn, 1972; Durr et al, 1980; Seow et al, 1985a) which may have a familial tendency. In addition, taurodontism has been documented as a manifestation of multiple-system malformation syndromes including the tricho-dento-osseous (TDO) syndrome (Lichtenstein et al, 1972), Klinefelter syndrome (Stewart, 1974), otodental dysplasia (Levin et al, 1975), ectodermal dysplasia (Stenvik et al, 1972) and Down syndrome (Jaspers, 1981).

However, although missing teeth may be an associated feature in many of the cases of taurodontism cited in the literature, there have been no previous studies investigating the prevalence of taurodontism in hypodontia in general. As an ectodermal origin has been suggested for both taurodontism (Jorgensen, 1982; Hamner et al, 1964) as well as hypodontia (Barjian, 1960), it is likely that these two traits may be associated. Further support

of this concept is the fact that taurodontism may be also observed in amelogenesis imperfecta (Witkop and Sauk, 1971), a defect of ectodermal origin. In this study the author investigated the prevalence of taurodontism in a group of children with hypodontia compared to a control group with full permanent dentitions. To establish the diagnosis of taurodontism objectively, a novel biometric technique was employed.

MATERIALS AND METHODS

Patients with hypodontia

Random screening of 1032 patient records which included panoramic radiographs from the pedodontic clinic at the University of Queensland Dental School revealed that 66 patients (6.4%) had agenesis of at least one tooth. There were 37 males and 29 females and their mean age at the time of radiography was 11.08 ± 2.9 years (range 5-19 years). All the patients were Caucasian and had hypodontia as an isolated trait, and did not suffer these defects as part of an overall syndrome.

Control patients

For every patient with hypodontia, a control was selected, who matched the study case for the age at which the panoramic radiograph was taken, as well as sex. All control patients were shown to have a full permanent dentition from the radiographs. In addition, they did not suffer from any defects which may be features of medical syndromes.

Selection of molar tooth for measurement

The mandibular first permanent molar was selected as the tooth for analysis for several reasons. Firstly, the first molar is considered the most stable tooth of the series, hence any change in its morphology may indicate a true change of the molar series. In particular, the cuneiform single-rooted molar which is not considered a form of taurodontism (Blumberg et al, 1971) is rarely seen in the first molar, thus eliminating possible errors from misdiagnosis. Secondly, the entire outline of this tooth is usually clearly evident on the panoramic radiograph in contrast to the first permanent maxillary molar in which the root apices are usually obscured by the zygomatic bone. Thirdly, the first permanent molar is usually the only fully developed molar in the age group under study.

Tooth measurements

The outline of the mandibular first permanent molar teeth was first traced from the panoramic radiograph onto transparent paper from which measurements were taken. The parts of each tooth comprising the crown, body and root were identified using the following definitions: Crown (C) - from the deepest part of occlusal surface to the cementum-enamel junction; Body (B)- from the cementum-enamel junction to the root furcation; Root (R) - from the root furcation to the apices (Keith, 1913; Shaw, 1928; Mena, 1971). Figure 8.1 shows these anatomical divisions on a taurodontic molar.

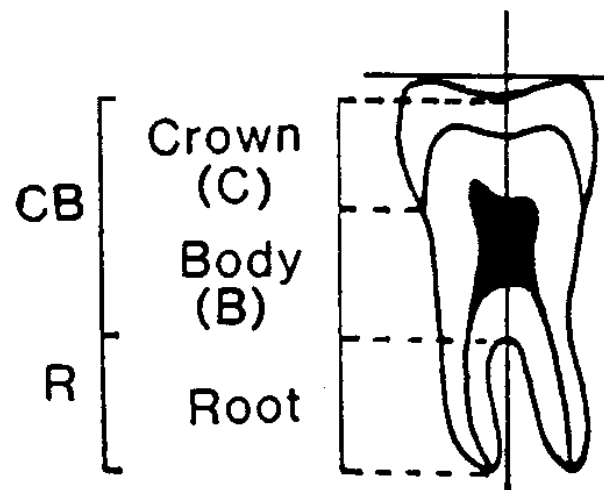


Figure 8.1 Measurements of crown and root lengths on a mandibular first permanent molar. The crown-body (CB) length was determined by drawing an occlusal line through the deepest pit which is parallel to another line joining the cusp tips. The length was determined along a vertical axis drawn at right angles to the occlusal line measured from the deepest pit to the furcation. Similarly, the length R was determined along the same vertical axis from the furcation to the root apex.

The lengths of the crown plus body (CB) as well as the root (R) were measured as shown in Figure 8.1. The CB of the tooth was determined by drawing an occlusal line through the deepest pit which is parallel to another line joining the cusp tips (Fig. 8.1). The length was determined along a vertical axis drawn at right angles to the occlusal line measured from the deepest pit to the furcation. Similarly, the length R was determined along the same vertical axis from the furcation to the root apex.

Validation of method

As panoramic radiographs may be associated with distortions (Pilo, 1987; Balis, 1981), we compared the accuracy of the images of mandibular first permanent molars on the panoramic radiographs with the images of the same teeth on periapical radiographs taken with the parallel long-cone technique. The radiographs of twenty patients (11 females, 9 males) who were not part of the study population were used for analysis. All these patients had a panoramic radiograph taken at about the same time as a long-cone periapical radiograph of a mandibular first permanent molar. As the latter technique is associated with minimal distortion, comparison of CB:R ratios in the mandibular first molar between the two techniques may determine possible discrepancies due to distortion on the panoramic radiographs.

The results are shown in Table 8.1. The paired t-test revealed that the mean difference in CB:R ratio in the mandibular first molar between the two techniques was not statistically

Table 8.1. Comparison of the crown-body to root ratios (CB:R) using panoramic (PAN) vs periapical (PA) long cone techniques

Patient No.	CB:R of mandibular first permanent molar		Difference in CB:R (PAN minus PA)
	Panoramic (PAN)	Parallel Technique Periapical (PA)	
1	0.76	0.77	-0.01*
2	1.05	1.10	-0.05
3	1.26	1.29	-0.03
4	0.93	1.00	-0.07
5	0.95	1.00	-0.05
6	1.04	1.05	-0.01
7	0.75	0.88	-0.13
8	0.81	0.95	-0.14
9	1.00	1.00	0.00
10	0.91	0.94	-0.03
11	0.94	0.95	-0.01
12	1.00	1.00	0.00
13	1.27	1.22	+0.05
14	0.79	0.82	-0.03
15	0.93	0.90	+0.03
16	1.09	1.03	+0.06
17	0.74	0.74	0.00
18	0.79	0.82	-0.03
19	0.93	0.90	-0.03
20	1.09	1.03	+0.06
Mean \pm SD	0.95 \pm 0.15	0.97 \pm 0.13	-0.02 \pm 0.06

The paired t-test shows that mean difference between the two techniques is not statistically significant ($t=-1.49$, $df=19$, $p=0.15$)

* The sign test reveals that the number of negative values is not significant, $p=0.30$.

significant ($p=0.30$), indicating that for this tooth selected, the panoramic radiograph is closely equivalent to the long-cone periapical radiograph.

Statistical analysis

The paired t-test, Chi-square test as well as Fisher's exact test, as appropriate, were used for statistical analysis of the data.

RESULTS

Prevalence of taurodontism in hypodontia and control groups

Table 8.2 shows the prevalence of taurodontism of the mandibular first permanent molar in the hypodontia group compared with the control group. As shown in the table, taurodontism was diagnosed in 34.8 percent of hypodontia patients compared with only 7.5 percent of control, the difference being statistically significant ($p < 0.001$).

The prevalence of taurodontism was further analysed according to sex (Table 8.3). As shown in the table, there was no significant difference in prevalence between the sexes in both the hypodontia and control groups.

Prevalence of various classes of taurodontism

For the diagnosis of a normal or cynodont tooth (Keith, 1913), a CB:R ratio of 1:1 is reasonable as it has been suggested

Table 8.2. Prevalence of taurodontism in patients with hypodontia compared to controls.

Taurodontism of 1st permanent molar	No. of patients	
	Hypodontia (n = 66)	Control (n = 66)
Present	23 (34.8%)*	5 (7.5%)
Absent	43 (65.2%)	62 (92.5%)

* $\chi^2 = 14.99$, $df = 1$, $p < 0.001$

Table 8.3. Prevalence of taurodontism according to sex

		Taurodontism Present	
		Hypodontia	Control
Males	(n=37)	13 (35.1%)*	3 (8.1%)
Females	(n=29)	10 (34.5%)	2 (6.9%)

Figures in parentheses represent percentages of the total numbers of males and females in each group.

that the length of the roots of a normal molar is at least equal to the crown-body length (Keith, 1913). This concept was confirmed in preliminary measurements of molars subjectively classified as normal in our preliminary investigations. However, to exclude misdiagnosis due to slight inaccuracies of measurements and radiographic distortions, a CB:R ratio of slightly less than 1:1.0, i.e. $<1:1.1$ was considered to be within normal limits.

According to Shaw (1928), taurodontism occurs in varying degrees which may be classified in increasing order of severity as hypotaurodontism, mesotaurodontism and hypertaurodontism. As these distinctions were usually subjectively determined previously, we attempted an objective classification based on the CB:R ratio.

Mandibular first permanent molars were first subjectively classified into the 3 groups by visual examination of panoramic radiographs. Mean CB:R ratios were obtained for each putative group of taurodontism. From these preliminary measurements, it was determined that CB:R ratios of the range 1.10 - 1.29 be classified as the hypotaurodont group, those in the range 1.30-2.00 as the mesotaurodont group and those > 2.00 as the hypertaurodont group. Figure 8.2 shows a diagrammatic representation of these classes of taurodontism.

The prevalence of the 3 groups of taurodontism based on the above classification is shown in Table 8.4. As seen from the

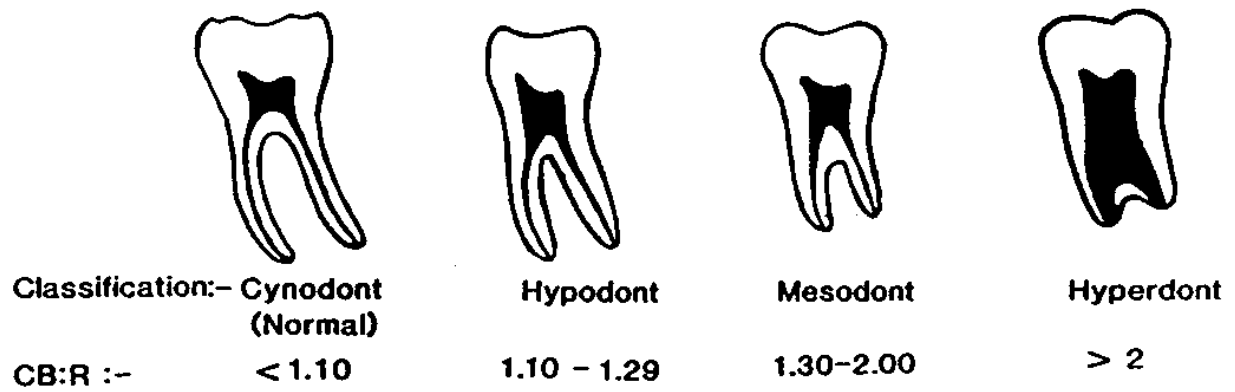


Figure 8.2

Diagrammatic representation of the 3 classes of taurodontism.

Table 8.4. Prevalence of various classes of taurodontic mandibular first permanent molars in hypodontia and control groups

Type of taurodontism	Crown & Body : Root (CB:R) ratio	No. of lower first permanent molar		p Value
		Hypodontia (n = 132)	Control (n = 132)	
Cynodont (Normal)	< 1.10	93 (70.5%)	125 (94.8%)	p < 0.001 ¹
Hypotaurodont	1.10 - 1.29	25 (18.9%)	6 (4.5%)	p < 0.001 ²
Mesotaurodont	1.30 - 2.00	13 (9.8%)	1 (0.8%)	p < 0.001 ³
Hypertaurodont	> 2.00	1 (0.8%)	0	N.S.

¹ $\chi^2 = 27.59$, df = 1

² $\chi^2 = 13.51$, df = 1

³ $\chi^2 = 11.04$, df = 1

table, 94.8 percent of mandibular first permanent molars were classified as normal (cynodont) in the control group compared to only 70.5 percent in the hypodontia group ($p < 0.001$). In the latter group, 18.9 percent of all the teeth analysed were classified as hypotaurodont, 9.8 percent as mesotaurodont and 0.8 percent as hypertaurodont. In contrast, in the control group, only 4.5 percent of all the teeth analysed were classified as hypotaurodont, 0.7 percent as mesotaurodont and no teeth showed hypertaurodontism. These differences in the prevalence of different classes of taurodontism between the 2 groups are statistically significant ($p < 0.001$).

Types of hypodontia associated with taurodontism

It is of interest to determine if taurodontism is associated with certain patterns of hypodontia. Table 8.5 shows the different types of hypodontia showing taurodontism in the mandibular first permanent molars. As seen from the table, 56.5 percent of patients with taurodontism had multiple missing teeth, 30.4 percent had missing premolars, 8.7 percent had missing lateral incisors and 4.3 percent had both lateral incisors and premolars missing. The differences in the results are statistically significant, ($p=0.003$, Fisher's exact test), indicating that taurodontism is strongly associated with multiple missing teeth and to a lesser extent, missing premolars.

Table 8.5. Types of hypodontia associated with taurodontism

Type of hypodontia (Mandibular + Maxillary)	No. of patients showing taurodontism in mandibular first molar
	(n = 23)
Isolated missing teeth (n=46)	
Central incisor (n = 1)	0
Lateral incisors (n = 20)	2 (8.7%)
Premolars (n = 21)	7 (30.4%)
Lateral incisors and premolars (n = 4)	1 (4.3%)
Multiple missing teeth* (n = 20)	13 (56.5%)

* The number of missing teeth varied from 6 to 22.

The differences in the results between the group of patients showing isolated hypodontia and the group with multiple missing teeth is statistically significant, $p=0.003$ (Fisher's exact test).

Occurrence of unilateral and bilateral taurodontism

The occurrence of taurodontism in mandibular first permanent molars in unilateral and bilateral cases was analysed in Table 8.6. As shown in the table, nearly half (47.8%) of the cases of taurodontism occurred bilaterally and the other half unilaterally. In the unilateral cases, there was no significant preference of left (30.4%) or right (21.7%) sides.

DISCUSSION

Since the first observation of cylindrical or prismatic teeth in prehistoric hominids (Keith, 1913) and in modern man (Pickerill, 1909), taurodontism has been of great interest to anthropologists, being thought by some as an atavistic trait (Hrdlicka, 1914) and by others as excluding Neanderthal man from the direct ancestral line of modern man (Boule and Vallois, 1957).

Shaw (1928) classified taurodontism into hyper-, meso- and hypo- types based on subjective criteria but there have been some attempts to define the trait objectively. Keene (1966) proposed a "taurodontism index" which compared the vertical height of the pulp chamber to the vertical height of the tooth portion containing the pulp to define the different classes of taurodontism biometrically. However, as pulp chamber size may alter due to environmental changes and ageing, Keene's technique was not considered useful (Stenvik et al, 1972). Blumberg et al (1971)

Table 8.6. Occurrence of unilateral and bilateral taurodontism in mandibular first molars

	Occurrence of taurodontism		
	Unilateral		Bilateral
	Left	Right	
	7	5	11
Percentage	30.4%	21.7%	47.8%

The above results are not statistically significant, $p > 0.01$

improved on Keene's technique by using metrical attributes which were thought to be stable and not influenced by caries, sex or age but subjective criteria were still employed for the development of their discriminant analysis and diagnosis of taurodontic teeth (Jaspers and Witkop, 1980).

In the present study the author developed a novel method of diagnosis of taurodontism in molars based on radiographic measurements of crown and body height to root length ratios. Although crown height may decrease with attrition, the method is simple to use and is suitable for young patients in whom there is minimal wear of the occlusal surfaces. In addition, the panoramic radiograph used in our method is usually available as part of routine clinical assessment in paediatric dentistry.

Using this method of analysis, we found that 34.8 percent of patients with hypodontia also showed taurodontism of at least one mandibular first permanent molar compared with only 7.5 percent of controls. Of great interest is the finding that in nearly half of the cases, taurodontism was observed unilaterally, in contrast to previous findings (Shifman and Chanannel, 1978). Figure 8.3 illustrates a typical patient showing taurodontic molars in association with missing teeth. In the present study, it was found that there was no sex preference in this trait. In addition, the severest forms of hypodontia with multiple missing teeth were most often associated with taurodontism. Of interest also is the fact that the prevalence figure in the control group

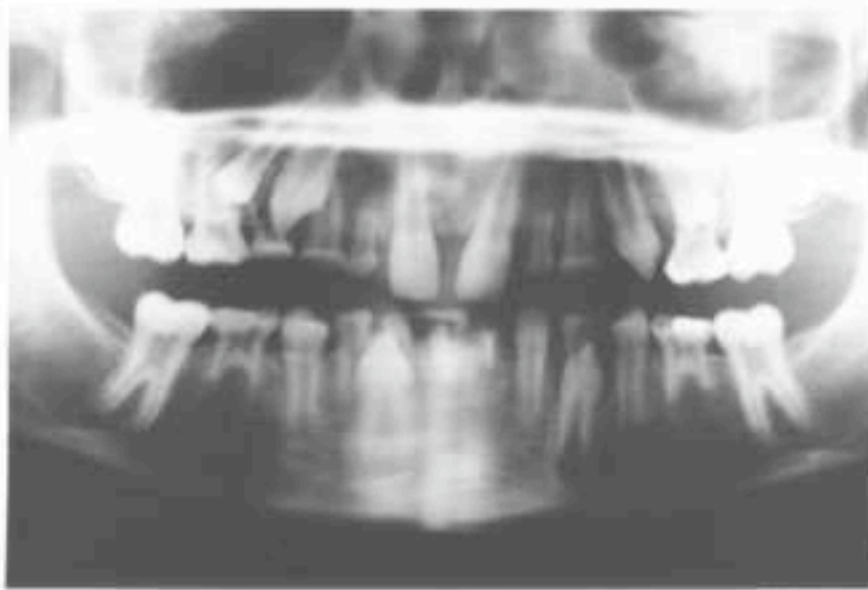


Figure 8.3

Panoramic radiograph of a typical patient in the study showing the association of missing teeth with taurodontic molars.

is within the range reported by other investigators using different methods of measurements and analysis. For example, a figure of 6.3 percent was reported in British school children (Holt and Brook, 1979) and Shifman and Chanannel (1978) mentioned that 5.6 percent of young Israeli adults aged 20 to 30 showed taurodontism. However, a lower prevalence figure was observed by Keene (1966) who found the trait in 3.4 percent of navy recruits. Blumberg et al (1971) reported a 2.5 percent prevalence in their study of Caucasian patients.

To the author's knowledge, there has been no previous study showing association of taurodontism in a large group of patients with hypodontia, even though taurodontism has been reported in many syndromes which also feature hypodontia (Seow et al, 1985a; Lichtenstein et al, 1972; Levin et al, 1975; Stenvik et al, 1972). As many of these syndromes involve ectodermal defects, it is possible that hypodontia and taurodontism may both be manifestations of an ectodermal defect. In addition, taurodontism is also observed in some types of amelogenesis imperfecta (Winter et al, 1969), an aberration of ectodermal origin. The present study showing the association of taurodontism with hypodontia thus further supports the concept that taurodontism probably results from an alteration in Hertwig's epithelial root sheath (Hamner et al, 1964) which is an ectodermal derivative.

Several clinical complications may result from the abnormal morphology of a taurodontic tooth. In endodontic therapy, the

extensive length of the pulp chamber may create difficulties in location of root canals and subsequent problems in cleaning and obturation. These difficulties are compounded by the presence of pulp stones and unusual apical root canal systems which often accompany taurodontism (Ogden, 1988).

In fixed prosthesis therapy it is reasonable to suggest that a taurodontic molar may not be considered an adequate abutment tooth due to its smaller surface area which may be less resistant to lateral displacing forces compared to cynodont teeth. By the same reasoning it may be suggested that exodontia of taurodontic molars should be easier compared to cynodont teeth, ~~however~~ , difficulties have been reported (Mangion, 1962).

It has been suggested that taurodontism may actually be advantageous from a periodontal aspect. This is due to the more apical location of the furcation which is less susceptible to be involved in periodontal disease.

In conclusion, the results of the present study showing the association of taurodontism with hypodontia indicate that clinicians should be alerted to the possibility of this unusual dental morphology in all patients with missing teeth.

CHAPTER NINE

PALMOPLANTAR HYPERKERATOSIS WITH SHORT STATURE,
FACIAL DYSMORPHISM AND HYPODONTIA:
A NEW SYNDROME?

INTRODUCTION

Hyperkeratosis of the skin may result from both acquired and hereditary causes. Acquired hyperkeratosis of the palms and soles may result from severe physical work, neurodermatitis, contact dermatitis, psoriasis, tertiary syphilis, fungal infections and arsenal keratoderma (Fred et al, 1964). Inherited types of palmo-plantar keratoderma are classified into a few groups based on the mode of inheritance and clinical presentations including dental features. The syndromes presenting with diffuse-type of hyperkeratosis are shown in Table 9.1.

In dentistry, the most well-known of these conditions is the Papillon-Lefevre syndrome which is inherited in an autosomal recessive manner and characterised by diffuse palmo-plantar hyperkeratosis and generalised rapidly progressive periodontitis resulting in the early loss of both deciduous and permanent dentitions (Gorlin et al, 1964; Haneke, 1979; Vrahopoulos, 1988). Less well known are the syndromes known as Mal de Meleda (Jee et al, 1985) keratosis palmaris et plantaris (KPP), also called the Unna-Thost syndrome or tylosis (Dencer, 1953; Stern et al, 1984) as well as the Richner-Hanhart syndrome, a form of tyrosinemia (Stern et al, 1984). These three conditions differ from the Papillon-Lefevre syndrome in that early loss of the teeth is not a notable feature. In addition, the Mal de Meleda and the Richner-Hanhart syndromes are inherited in an autosomal recessive

Table 9.1. Types of inherited diffuse forms of palmoplantar keratoderma.

Syndrome	Mode of Inheritance	Associated General Features	Dental Features
Papillon-Lefevre	Autosomal recessive	Hyperhidrosis Dysplastic nails Arachnodactyly Susceptibility to infections. Physical retardation Mental retardation Calcification in falx cerebri	Hyperkeratosis of attached gingiva Exfoliation of primary and permanent teeth soon after eruption
Mal de Meleda	Autosomal recessive	onychodystrophy	No oral findings reported
Keratosis Palmaris et Plantaris (KPP or tylosis)	Autosomal dominant	carcinoma of skin and esophagus Hyperhidrosis Dysplastic nails optic atrophy mental retardation oxycephaly, clubbing of fingers clinodactyly deafness	Hyperkeratosis of attached gingiva
Richner-Hanhart	Autosomal recessive	Tyrosinemia, corneal dystrophy, brachyphalanges, mental retardation	No oral findings reported
This report	Autosomal dominant	Small stature Facial dysmorphism Clinodactyly Dysplastic nails Deafness Epilepsy	Hypodontia Enamel hypoplasia Fusion of teeth Taurodontism Anterior open bite

manner which distinguish them from the Unna-Thost syndrome, an autosomal dominant condition (Bergfeld et al, 1982).

Review of the medical literature reveals that the autosomal dominant form of palmoplantar keratoderma is a heterogeneous group of disorders with many variants from the original syndrome described by Thost in 1880 and Unna in 1886 (Cockayne, 1933). In most of these variants as well as in the original syndrome, dental findings were unremarkable. In this study, a family with autosomal dominant palmoplantar hyperkeratosis accompanied by hypodontia is described. The facial dysmorphism and hypodontia present in this family suggest it to be a new syndrome.

INDEX CASE

The proband was a ten year-old Caucasian boy who was referred to the University Dental School by his pediatrician for dental assessment. His medical condition was at that time undiagnosed.

Birth and Neonatal History

The patient was the product of a non-consanguineous marriage, born 4 weeks premature after an uncomplicated pregnancy with breech delivery and birth weight of 1079 gm. Neonatal complications included respiratory distress requiring mechanical ventilation, inguinal hernia and undescended testes which were surg-

ically corrected. Absence of eye lashes, eyebrows and finger-nails was noted at birth.

Craniofacial Dysmorphism

The patient showed frontal bossing and hypertelorism (Fig.9.1). Hyperterlorism canthi was confirmed by measurements of the outer canthi and inner canthi which gave values of 9.5 cm and 3.5 cm respectively. These values were greater than 97th percentile for a 10 yr. old (Smith, 1982). The interpupillary distance was 5.8 cm which was between the 75th and 97th percentile for a 10 yr. old (Smith, 1982). In addition, abnormal hair whorls and a low posterior hair line were observed (Fig.9.1).

Skin

Moderate diffuse hyperkeratosis of the palms of the hands and soles of the feet was noted shortly after birth (Fig.9.2). In addition, hypoplasia of the nails was observed, ranging from severe hypoplasia in the fifth finger to mild hypoplasia in the others (Fig.9.2).

Musculoskeletal

The patient was of proportionate short stature with height 106.6cm (<3rd percentile), weight 17.6kg (<3rd percentile), and head circumference 49.5 cm (3rd percentile). Clinodactyly of the fifth finger on both hands was noted (Fig.9.2). A handwrist x-



Fig. 9.1. Facial photographs of proband showing hypertelorism, frontal bossing and low hair line.



Fig. 9.2. Hands and feet of proband showing palmoplantar hyperkeratosis. Clinodactyly of the fifth finger is also shown. Note hypoplastic finger nail.

ray at age 9 years 6 months revealed a delayed bone age of approximately only 4 years 6 months.

Neurological

Mild mental retardation was noted and the patient attended a special school. In addition, there was bilateral mild conductive hearing loss. Petit mal epilepsy was diagnosed recently with an EEG consisting of 8-9 cycles/second activity present bilaterally at 30-60 μ v. It was adequately controlled by carbamazepine.

Investigations

Metabolic screens of plasma and urine revealed no biochemical abnormalities. Banded chromosomal analysis was normal.

Dental Findings

Examination revealed that the patient had incompetent lips and a Class II malocclusion with overjet of 10mm and a large anterior open bite which was accompanied by an anterior tongue thrust habit present at rest position as well as during swallowing and speech.

Intra-oral examination (Fig.9.3) revealed the following teeth to be present :

16	55	54	53	52	21	62	63	64	65	26
46	85	84	83	41	31	32	73	74	75	36'

Mild enamel hypoplasia manifested as a depressed area of missing labial enamel was noted on the mandibular left central incisor and the left maxillary central incisor showed slight



Fig. 9.3. Intra oral photograph of proband showing the anterior teeth. Enamel hypoplasia of the mandibular left central incisor is evident.

diffuse enamel opacity. All other erupted teeth were clinically normal.

Periodontal examination revealed poor oral hygiene and marked gingivitis. Periodontal probing did not reveal any pockets greater than 3mm and no abnormal mobility was detected. In addition no hyperkeratinization of the gingiva was noted.

An orthopantograph (Fig.9.4) and occlusal radiographs (Fig.9.5) confirmed agenesis of the permanent maxillary lateral incisors and the mandibular right lateral incisor. In addition permanent first molars revealed radiographic evidence of slight taurodontism (Fig.9.4). These radiographs also showed all other permanent teeth to be developing normally. No abnormalities were noted from bitewing radiographs.

FAMILY STUDIES

Family Pedigree

A family pedigree chart showing 18 affected members spanning 4 generations is illustrated in Figure 9.6. In the present family the children have inherited the condition from the father and an autosomal dominant mode of inheritance with a high degree of penetrance is evident. Apart from the proband, his siblings and parents, the other family members were diagnosed from history, particularly in relation to palmoplantar hyperkeratosis.



Fig. 9.4. Orthopantograph of the proband illustrating the missing mandibular permanent right lateral incisor and the maxillary permanent lateral incisors.



Mark
let a
right
and indicate
with arrows
the shortest
distance in
the maxillary
teeth

Fig. 9.5. Mandibular and maxillary occlusographs of proband confirm the absence of the maxillary permanent lateral incisors and the mandibular right lateral incisor.

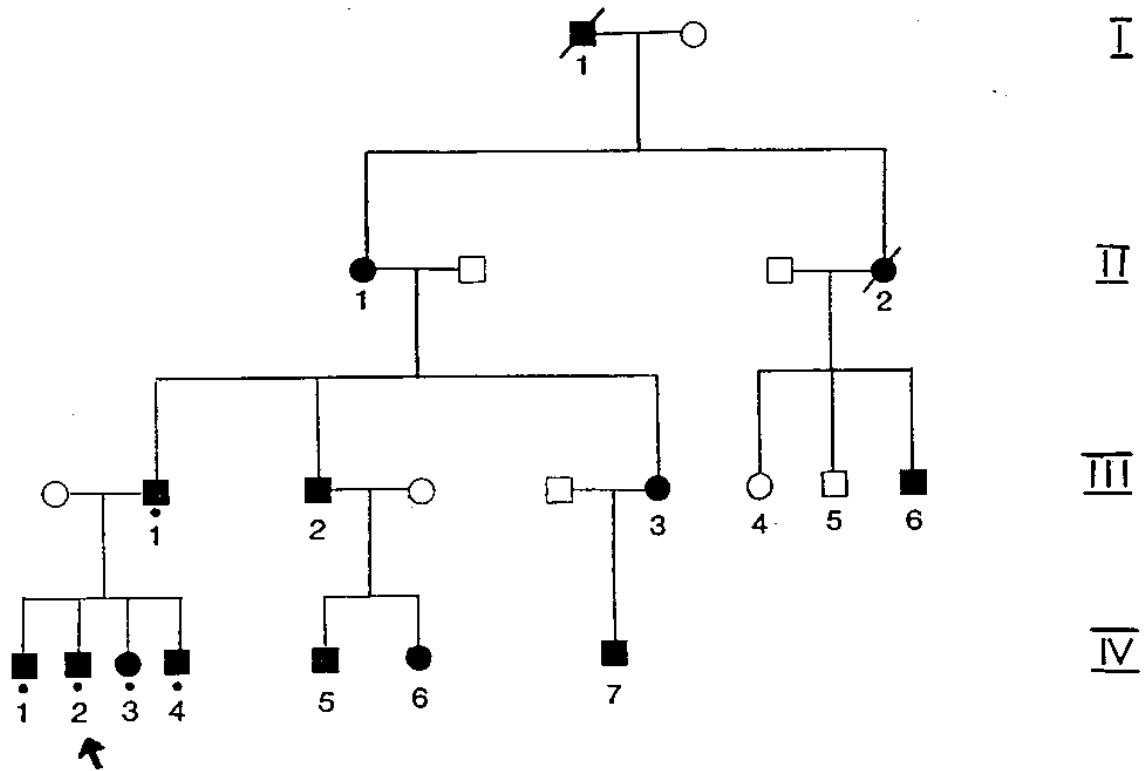


Fig. 9.6. Pedigree of the family (4 generations). Those members diagnosed from history all have palmoplantar hyperkeratosis which is a feature easily distinguished by non-professionals.

○ unaffected female
(by history)

● affected female
(by history)

● affected female
(by examination)

□ unaffected male
(by history)

■ affected male
(by history)

■ affected male
(by examination)

Siblings

The patient had 2 brothers aged 12 years and 3 years and a sister aged 4 years. All siblings presented for dental examination. The findings are shown in Table 9.2. Hyperkeratosis of the palms and soles appeared to be a prominent feature in all the siblings. Other dysmorphic features noted in the proband such as small stature, hypertelorism, clinodactyly, hypoplastic nails and low hair line were also noted in all the siblings. In addition, the oldest sibling aged 12 years shared further similar medical findings with the index case such as low birth-weight, premature birth and petit mal epilepsy.

Dental examination of the siblings revealed that all had agenesis of some of the permanent teeth. These missing teeth included mandibular incisors in both the brothers and maxillary lateral incisors in the sister. The oldest sibling also presented with a macrodont maxillary central left incisor which had a distinct labial groove from the gingival margin to the incisal edge (Fig.9.7). This feature together with the fact that the maxillary left lateral incisor was absent indicated that fusion of the central and lateral incisors may have occurred. Periapical radiographs which revealed a single large pulp chamber further suggest true fusion of the incisors. This sibling also showed enamel hypoplasia manifested as loss of enamel on the fused tooth surface as well as enamel opacities on the labial surfaces of both maxillary and mandibular central incisors and the permanent first molars.

Table 9.2. Clinical presentations of affected family members.

Dysmorphic Feature	Family Member				
	Father	Sib 1	Proband	Sib 2	Sib 3
Small stature		✓	✓	✓	✓
Hypertelorism		✓	✓	✓	✓
Hyperkeratosis of palms & soles	✓	✓	✓	✓	✓
Clinodactyly		✓	✓	✓	✓
Dysplastic nails		✓	✓	✓	✓
Low hair line		✓	✓	✓	✓
Abnormal hair whorls		✓			
Skin tags on ear					
Medical findings					
Low birth weight		✓	✓		
Prematurity of birth		✓	✓		
Deafness		✓	✓		
Epilepsy	✓	✓	✓		
Dental findings					
Missing teeth		✓	✓	✓	✓
Taurodontism		✓	✓		
Enamel hypoplasia		✓			
Fusion of teeth			✓		
Anterior open bite			✓		
Tongue thrust					



Fig. 9.7. Anterior teeth of 1st sibling showing fused maxillary permanent left central and lateral incisors and the missing mandibular permanent lateral incisors.

Mother

The mother (aged 34 years) who wore a partial upper denture had only a few teeth at examination, the others having been lost through dental decay. Apparently she had complete sets of primary and permanent teeth and there was no family history of agenesis of the teeth.

Father

The father aged 36 years presented with marked diffuse hyperkeratosis of the palms and soles which had been present since birth. He also suffered mild epilepsy, mild hypertension which does not require treatment, and chronic bronchitis from cigarette smoking. He was of normal stature (height 154.0cm) but over-weight (107kg) and no craniofacial dysmorphological features were noted. Dental examination revealed all permanent teeth to be present except for the mandibular left second and third molars. According to the patient, these teeth were extracted for extensive caries. Unrestored proximal caries was noted in several teeth. Periodontal probing revealed the presence of generalised pockets of over 5mm around most teeth and several teeth had moderate mobility. A diastema was noted between the maxillary central incisors. A Class II malocclusion was present with increased overbite and overjet.

DISCUSSION

Palmoplantar hyperkeratosis is a feature of many acquired and genetic disorders. Inherited conditions are usually identified by their mode of inheritance, phenotype and associated features because the underlying defect is seldom known (Demis et al, 1982; Der Kaloustian and Kurban, 1982).

Dental abnormalities may be important diagnostic features in many of these conditions as in other syndromes (Seow et al, 1985a; Seow and Latham, 1986; Gorlin et al, 1976). For example, in two autosomal recessive types of hyperkeratosis, different dental presentations are noted. In the Papillon-Lefevre syndrome, severe periodontitis and premature loss of both dentitions are constant findings whereas in the Mal de Meleda disorder, the teeth are apparently normal (Jee et al, 1985). Also severe enamel hypoplasia was noted in a new autosomal dominant type of palmoplantar hyperkeratosis associated with corneal changes, short stature, brachydactyly and premature birth reported by Stern et al (1984). However, hypodontia has not been associated with the autosomal dominant form of palmoplantar hyperkeratosis before, although it has been reported in autosomal recessive forms of hyperkeratosis associated with ectodermal dysplasia (Egelund & Frentz, 1982).

In the present study, hypodontia, enamel hypoplasia, craniofacial dysmorphism, deafness, small stature, epilepsy and

clinodactyly are associated with an autosomal dominant form of palmoplantar hyperkeratosis. As hypodontia and craniofacial dysmorphism have not been associated with palmoplantar hyperkeratosis before, the present family may represent a new genetic syndrome. Searches carried out on two dysmorphology computer databases (The London Dysmorphology Database, by Winter, R & Baraitser, M and Pictures of Standardised Syndromes and Undiagnosed Malformations by Murdoch Institute for Research into Birth Defects, Melbourne, Australia) did not reveal any similar syndrome reported previously.

The apparent lack of facial dysmorphism and hypodontia in the father may indicate variability in expressivity of the phenotype in this syndrome. It is also possible that hypodontia may be inherited as an isolated trait. However, as skin and teeth are both ectodermally-derived, it is most likely that in this case, hypodontia is related to the hyperkeratosis condition.

As the present condition is inherited in an autosomal dominant manner, it may represent a variant of the Unna-Thost syndrome. This condition is also known as keratosis palmaris et plantaris (KPP) or tylosis (Dencer, 1953). However, large studies on patients classically affected by the Unna-Thost syndrome (Nielsen, 1985a) did not report other defects associated with the disorder apart from squamous cell carcinoma of the oesophagus and skin (Shine and Allison, 1966; Howell-Evans et al, 1958; Yesudian et al, 1980) and dermatophytosis (Nielsen, 1985(b)).

A study of current literature on the autosomal dominant forms of palmoplantar hyperkeratosis reveals a few other conditions which could possibly be related to the present syndrome. Stern et al (1984) reported on an autosomal dominant syndrome characterised by unique corneal epithelial changes, diffuse palmoplantar hyperkeratosis, distal onycholysis, brachydactyly, short stature, premature birth and severe enamel hypoplasia. Also, clinodactyly associated with the autosomal dominant form of palmoplantar hyperkeratosis was found in the families studied by Aguirre-Negrete et al (1981), Hernandez et al (1982) as well as Anderson and Klintworth (1961). In addition, deafness has also been reported in 10 cases in one family showing the autosomal dominant palmoplantar hyperkeratosis by Bititci (1975), as well as by Hatamochi et al (1982).

Metabolic disorders such as tyrosinaemia type 2 (tyrosinosis, Richner-Hanhart syndrome) produce palmoplantar hyperkeratosis; however, these conditions were excluded in the present family from metabolic studies and lack of corneal opacities as well as the fact that these conditions are usually inherited in an autosomal recessive manner.

In conclusion, this possibly new syndrome further expands the panorama of diverse clinical conditions presenting with palmoplantar hyperkeratosis.

CHAPTER TEN

THE PREVALENCE OF FURCATION CANALS IN PRIMARY MOLARS

INTRODUCTION

The furcation area of a molar tooth which encompasses the region around the division of the roots, is of special significance in the primary dentition due to its close anatomical relationship with the follicle of the succedaneous permanent molar. Accessory canals in the furcation area are clinically important for several reasons. Infection in the pulp can spread through these channels to affect the interradicular bone before involving perapical tissues (Winter, 1962; Myers et al, 1987). In addition, medicaments placed in pulp can enter furcation bone through these channels. These accessory canals also provide communication of the pulp with periodontal tissues, often being the cause of deep periodontal pockets associated with non-vital teeth (Seltzer et al, 1963). Although the clinical implications of these communication channels are well recognised, there has been very little research showing their existence as well as the anatomical location of these furcal foramina, particularly in primary teeth. This study was performed to determine the prevalence and location of accessory canals in the furcation region of extracted primary molars.

MATERIALS AND METHODS

Selection of teeth

Seventy-five extracted primary molars which had been previously stored in 2 percent formalin were selected at random.

Although the reasons for the extractions of the teeth were unknown, the teeth were carefully selected by the criterion that root resorption had not involved more than a third of the apical aspect of any root.

Preparation of teeth

The teeth were prepared according to the method of Gutmann (1978) with slight modifications. They were first placed in a solution of 2.5 percent sodium hypochlorite for surface cleansing for twenty minutes, followed by rinsing with tap water. An occlusal endodontic access cavity was prepared in each tooth, followed by standard endodontic techniques of pulp tissue removal using spoon excavators and broaches. Care was taken not to scrape the floor of the pulp chamber. The teeth were stored in 3 percent hydrogen peroxide for 1 week, the solution being changed every two days. This technique destroys tissue attachment to the tooth, allowing for easy debridement but does not cause decalcification (Hibbard and Ireland, 1957). The teeth were rinsed in tap water for 20 minutes and immersed in 95 percent alcohol for 24 hours to fix the tissues. Finally, they were dried thoroughly using compressed air before being placed in a vacuum suction system for dye penetration of the pulp system.

Dye penetration under vacuum suction

A tube was modified from a 3cm by 1cm rubber teat⁺. One end was placed around the crown of each tooth (Fig 10.1) to achieve a

⁺ Ansell International, Dandenong, Victoria, Australia



Figure 10.1. Primary molar tooth assembled for dye penetration of the root canals.

A rubber test holds the tooth securely at one end to achieve a tight seal. The other end of the test is sealed around a plastic tube through which the dye is inserted. A wire tie is used to seal this section securely. Red sticky wax has been applied to the apices of the tooth.

tight seal. The other end was sealed around a plastic tube modified from a 1cm disposable pipette tip* and the joint was secured using a piece of 0.18 mm wire tie (Fig 10.1). The plastic tube was located centrally in a 4cm diameter rubber stopper designed to fit a 2 litre flask attached to a vacuum pump (Fig 10.2). Red sticky wax was applied to the apical one-third of each root to seal the apical foramen (Fig 10.3). A drop of Safranin dye (red)** was introduced down the tube into the pulp chamber using a fine disposable glass pipette. Extreme care was taken to ensure no spillage of dye occurred onto the external aspects of the tooth. A vacuum pressure of 550 mbar was applied to the external root surfaces for a maximum of 5 minutes. The furcation area of each tooth was observed carefully as soon as the vacuum was applied for the appearance of any red staining. The tooth was removed as soon as red staining was noted so that markings on the cemental surfaces remained discrete.

Statistical Analysis

The Chi-square test, as well as exact calculations based on the binomial distribution, where appropriate, were used for statistical analysis of the data.

* Monoject Scientific, Sherwood, St. Louis, MO, USA

** Sigma Chemical Co., St. Louis, MO, USA



Figure 10.2. The vacuum suction apparatus for dye penetration of root canals.



Figure 10.3. Accessory foramen localised in the furcation of a mandibular primary first molar.

RESULTS

Prevalence of foramina in the furcation region

It is important to define the anatomical areas under study. The "furcation" has been defined as the area limited to the immediate region where the roots separate while the "furcation region" encompasses the actual furcation of each tooth plus an area 4mm down the internal aspect of the root surfaces (Gutmann, 1978). Using these definitions, we first surveyed the prevalence of foramina in the furcation region of 75 primary molars. Overall, there were 32 teeth showing presence of foramina in the furcation region, giving a prevalence of 42.7 percent (Table 10.1). This prevalence varied slightly among the different teeth surveyed (Table 10.1). As shown in the table, the prevalence of foramina in the furcation region ranged from 33.3 percent in the mandibular first primary molar to 40.0 percent in the mandibular second molar, 48.0 percent in the maxillary second primary molar, and 50.0 percent in the maxillary first primary molar. The difference in prevalence among the different molars is not statistically significant ($p>0.1$).

Location of furcation foramina

It is of interest to analyse the location of the foramina. Table 10.2 shows the distribution of the foramina in the furcation region of the molars. As shown in Table 10.2, there were no significant differences in the location of the foramina ($p>0.1$) in both maxillary and mandibular first primary molars as well as the maxillary second primary molar. In contrast, in the mandi-

Table 10.1. Prevalence of foramina in the furcation region of primary first and second molars.

	First Primary Molar		Second Primary Molar		Total
	Max. (n = 10)	Mand. (n = 10)	Max. (n = 25)	Mand. (n = 30)	(n=75)
No. with furcal foramina	5	3	12	12	32
Percentage	50.0%	33.3%	48.0%	40.0%	42.7%

The difference in prevalence of furcal foramina among the different molars is not statistically significant ($p>0.1$).

Table 10.2. Analysis of location of foramina in the furcation region in primary molars.

Tooth	Location of Foramina		p value ⁺
	Furcation [*]	Furcation region**	
<u>First Primary Molar</u>			
Max. (n = 5)	2 (40.0%)	3 (60.0%)	1.0
Mand. (n = 3)	2 (66.7%)	1 (33.3%)	1.0
<u>Second Primary Molar</u>			
Max. (n = 12)	3 (25.0%)	9 (75.0%)	0.15
Mand. (n = 12)	2 (16.6%)	10 (83.4%)	0.04

* Furcation encompasses the immediate root division region

** Furcation region includes the internal aspect of the root from root division area down to approximately 4 mm of root length

+ The probability values were exact calculations based on binomial distributions

bular second primary molar, there was a greater percentage of foramina located in the furcation region compared to the furcation itself (83.4% vs 16.6%, $p=0.04$). Figure 10.3 shows a mandibular primary first molar with a foramen in the furcation as indicated by the discrete stained spot. In contrast, Figure 10.4 shows a foramen in the furcation region of a primary mandibular second molar.

Roots showing foramina in furcation region

It may be clinically relevant to identify the roots in furcation regions showing foramina in the primary molars. Table 10.3 shows the roots involved in the mandibular primary molars. The most commonly involved root in these teeth was the distal root (45.5%) followed by the mesial root (36.3%) and the involvement of both mesial and distal roots (18.2%). However, these differences were not statistically significant ($p>0.1$). Table 10.4 shows a similar analysis of the roots involved in the maxillary molars. The mesiobuccal root was most frequently involved (41.7%) with another 41.7 percent showing the presence of foramina in both mesiobuccal and palatal root surfaces. Only 16.6 percent showed the presence of foramina in the distobuccal root alone and no teeth had foramina on the palatal root.

It is of interest to note that diffusion of the dye through dentinal tubules was not a problem.



Figure 10.4. Accessory foramen noted in the furcation region of a mandibular primary second molar.

Table 10.3. Type of root showing foramina in the furcation region* in mandibular primary molars.

Root	No of teeth with foramina (n = 11)
Distal alone	5 (45.5%)
Mesial alone	4 (36.3%)
Distal and Mesial	2 (18.2%)

* These foramina are located on the internal aspect of the root within 4 mm from the centre of the true furcation area.

The differences in the results are not statistically significant ($p > 0.1$).

Table 10.4. Type of root showing foramina in the furcation region* in maxillary primary molars.

Root Surface	No of teeth with foramina (n = 12)
Mesiobuccal alone	5 (41.7%)
Distobuccal alone	2 (16.6%)
Palatal alone	0
Mesiobuccal and Palatal	5 (41.7%)

* These foramina are located on the internal aspects of the root within 4 mm from the centre of the true furcation area.

DISCUSSION

Accessory canals on root surfaces may be considered developmental aberrations caused by the persistence of abnormally placed blood vessels which leave gaps in the Hertwig's sheath (Scott and Symons, 1971). Although accessory canals may occur anywhere along the root surface, those in the furcation areas of molars pose the most difficult complications in clinical dentistry. Most of the previous work investigating the furcation region of teeth have centred on permanent molars. In these teeth, a wide range of prevalence figures of accessory canals have been noted, probably due to differing sensitivity of the techniques employed. Using a dye penetration method similar to that of the present study, Gutmann (1978) found that 24.5 percent of 102 permanent molars showed patent accessory canals leading from the floor of the pulp chambers to the furcation. However, a higher prevalence of 40 percent was noted by Vertucci and Williams (1974) in their visual examination of 100 mandibular first permanent molars using a dissecting microscope. The highest prevalence (59%) was noted by Lowman et al in 1973 using a combination of radiopaque dye system and radiography on 46 permanent molars.

In sharp contrast, other investigators employing chiefly radiographic methods found no lateral canals coming from the pulp chamber of multirooted teeth (Hession, 1977; De Deus, 1975; Pineda and Kuttler, 1972). This is probably due to low sensi-

matory potential (Seow and Thong, 1986) and if allowed to contact bone, may cause osteitis. Therefore, it is advisable to localise the area of application of pulpotomy medicaments to the amputated root stump, rather than spreading it over the entire pulpal floor, where there is a high possibility of diffusion of the medicaments through accessory canals into the alveolar bone.

Thirdly, the communication of the periodontal tissues with the pulp effected by furcation canals may suggest that infections originating from the periodontal tissues could theoretically reach the pulp. Although periodontal abscesses are uncommon in children, they may be observed around ill-fitting stainless steel crowns, orthodontic bands as well as impacted foreign bodies. However, the prevalence of pulpal necrosis resulting from such periodontal infections are unknown.

In conclusion important clinical implications are associated with the high prevalence of accessory canals in the furcation region of primary molars.

CHAPTER ELEVEN

DISCUSSION

DISCUSSION

GENERAL INTRODUCTION

The work in the thesis was done to explore the clinical significance of developmental dental anomalies in paediatric dentistry. Due to limitations of available clinical material, only representative entities of each major type of dental anomaly were studied. Developmental enamel defects were investigated in prematurely-born, low birth-weight children in a controlled study which showed that the prevalence of enamel hypoplasia varied directly with birth weight i.e. the lower the birth weight, the greater the predisposition to enamel hypoplasia. Possible aetiological factors were explored, and deficiency of mineral stores appeared to be significantly associated with enamel hypoplasia, although laryngoscopy and endotracheal intubation were found to be important causes of localised left-sided maxillary anterior defects.

The dentition in vitamin D-resistant rickets was studied as an example of an inherited defect of dentine. A relatively large series of affected patients was studied and a clinical grading of the dental manifestations introduced to aid clinical diagnosis and management. Histological studies of affected teeth correlated with the clinical grading, and provided further information on the medical and genetic influences on dental manifestations of this condition.

In addition to developmental defects of enamel and dentine, abnormalities of tooth number and morphology were also investigated. Hypodontia, a relatively common anomaly, was studied in relation to various other dental anomalies that may be associated with it. Taurodontism was one such anomaly found to occur commonly with hypodontia; its diagnosis from radiographs of young patients was established with a novel biometric method.

Also, the manifestations of hypodontia and taurodontism in a patient with a previously undescribed systemic syndrome were presented to illustrate the importance of dental anomalies in syndrome identification. Finally, the prevalence of accessory root canals in the furcation region of primary molars were investigated. A high prevalence of 42.7 percent was observed, indicating their potential clinical significance.

In the following sections, the results of the studies in this thesis are brought into perspective in the light of current understanding of the clinical significance of these dental anomalies. For clarity, each group of developmental anomalies is discussed in a separate section.

ORAL COMPLICATIONS OF PREMATURE BIRTH

Introduction

A premature birth as defined by the World Health Organization occurs prior to 37 weeks gestation. Prematurely-born children usually have birth weights much less than the average of approximately 3333g, the most premature infants generally having the lowest birth weights. Survival rates of premature infants vary with birth weight, from a high of 98 percent for those with birth weights of 2000 to 2500g to a low of 26 percent for those with birth weights below 750g (Hack et al, 1979).

Serious sequelae may result from premature births. Follow-up studies of very low birth-weight infants(<1500g) have shown that 5 percent of such children have physical handicaps and approximately 4.5 percent have significant intellectual and/or neurological handicaps (Tudehope et al, 1983).

Enamel hypoplasia in prematurely-born children

Interest in the dental defects of prematurely-born children was first stimulated by the study of Stein (1936) who found that 41.7 percent of his pre-term patients showed defective teeth. Later studies by other investigators gave prevalences of enamel defects ranging from 20 percent (Forrester and Miller, 1955) to 77 percent in a histological study (Kreshover et al, 1958). The earlier investigations were done using children of higher birth weights of over 2500g because those with lower birth weights of less than 2000g did not survive.

With increasing sophistication of neonatal care in recent years, there has been a great increase in survival rates of infants born weighing less than 1500g, and the more recent studies have included such children (Funakoshi et al, 1981; Mellander et al 1982; Seow et al, 1984a; 1984b; Johnsen et al, 1984; Pimlott et al, 1985).

However, while previous studies have indicated that prematurely-born, low birth-weight children are extremely prone to develop enamel hypoplasia, only one controlled study (Seow et al, 1987; Chapter 2, this thesis) has shown conclusively that the prevalence of enamel defects varied directly with birth weight. In this study, 62.3 percent of VLBW

(<1500g) children showed developmental enamel defects compared to 27.3 percent of LBW children (1500-2500) and 12.8 percent of normal birth-weight children.

An interesting finding from this study is that LBW children show a prevalence of enamel defects comparable to earlier studies (Grahnen et al, 1974; Rosenzweig and Sahar, 1962; Mellander et al, 1982) on prematurely-born children who were all of this birth-weight group. However, the prevalence figure for the VLBW group is higher than that found in the study of Johnsen et al (1984) which is one of the few other studies using this birth-weight group. The discrepancy may be due to differences in patient care practices in different hospitals, as well as to differences in patient sampling and diagnostic criteria for dental defects.

Of further interest is the finding that there are discrepant values given for the prevalence of enamel defects in the normal children for the few studies which included these children for comparison. In the study by Seow et al (1987; Chapter 2, this thesis), 3 (6.4 %) out of 47 normal control children showed enamel hypoplasia and a further 3 (6.4 %) had enamel opacities, giving a total prevalence figure of 12.7 percent. This figure compares closely with the 13.1 percent observed in the study of Grahnen and Larsson (1958), but is markedly different from the 1.2 percent reported in the study of Rosenzweig and Sahar (1962), as well as the 26.0 percent in the study of Johnsen et al (1984) and the 39.6 percent in that of Mellander et al (1982). The reasons for the great discrepancies may be due firstly, to differences in patient acceptance rates. For example, in the study of Mellander et al (1982), the acceptance rate by normal

patients was exceptionally low, at only 30.9 percent, giving rise to the possibility of sampling errors. In contrast, in the study of Seow et al (1987; Chapter 2, this thesis), the acceptance rate was 97 percent for the normal control patients and 100 percent for both the VLBW and LBW children, hence the possibility of sampling errors was low.

Secondly, subjects from a clinic population cannot be considered suitable comparison groups as these patients may have greater dental problems compared to a randomly-selected group of children. Thus the high prevalence of defects seen in the control group in the study of Johnsen et al (1984) may be also due to this reason. However, in the study of Seow et al (1987; Chapter 2, this thesis), the control children were selected at random from the birth register of children born during the same period as the children under investigation, and at the same hospital; thus they represented a more valid comparison group.

Generalised enamel defects

Aetiological factors involved in the pathogenesis of generalised enamel defects in prematurely-born children are most likely related to systemic factors which are discussed in the following sections.

(i) Systemic factors suffered by prematurely-born infants

An infant born prior to full term is usually poorly equipped for extrauterine life, and requires considerable medical support in the neonatal period. Many serious complications are encountered in nearly all the organ systems.

Respiratory conditions present major challenges. These include birth asphyxia which results from failure of the premature infant to expand the lungs and establish effective ventilation and perfusion in the minute following birth due to an immature respiratory centre (Milner and Greenough, 1988). Respiratory distress syndrome or hyaline membrane disease is another common respiratory problem. This results from a lack of surfactant in the alveoli causing poor alveolar expansion with impairment of gaseous exchange (Gitlin et al, 1987).

Another serious systemic problem encountered in prematurely-born children is intracranial haemorrhage. It may result from birth trauma, perinatal hypoxia, as well as arteriovenous malformations and is associated with significant mortality and morbidity (Milhorat, 1981).

Patent ductus arteriosus (PDA) is also commonly observed in premature infants at a prevalence of 25 percent in all infants < 1500g birth-weight, and half of this number develop congestive cardiac failure (Kitterman et al, 1972). Although the avoidance of hypoxia, overhydration, respiratory distress syndrome and hypocalcaemia decreases the incidence of PDA (Raju et al, 1987), many premature infants still require induction of PDA closure with indomethacin or surgical intervention (Fyler and Lang, 1981).

Haematological problems are often encountered in prematurely-born infants. Anaemia is common and coagulation disorders may result from immaturity of the clotting mechanism. In addition, disseminated intravascular coagulation is a recognised complication of an increasing variety of neonatal conditions including septicaemia, shock, severe birth

asphyxia, respiratory distress syndrome and infections (Karpatkin, 1971).

A large group of metabolic disturbances may be experienced by premature infants due to immaturity of homeostatic mechanisms. These include hypocalcaemia, hypoglycaemia, hypomagnesaemia, hypernatraemia and hyperkalaemia. With improved understanding of the pathogenesis and early diagnosis, many of these conditions are now averted by effective preventive regimens. For example hypocalcaemia and neonatal tetany are now prevented by calcium supplements in the neonatal period.

- (ii) Difficulty in identifying individual systemic factors involved in the pathogenesis of enamel hypoplasia

Since the high prevalence of enamel defects in prematurely-born children was first noted, several investigators have attempted to identify perinatal and neonatal factors that may be involved in the pathogenesis of these defects. However, most of these attempts were unconvincing for many reasons. Firstly, single factors have been considered in isolation without taking into account many other systemic conditions that occur concurrently in prematurely-born children. In addition, if the control children selected for comparison are of normal birth weight and show only a small prevalence of enamel defects, it is not difficult to prove that a particular systemic condition singled out in prematurely-born, low birth-weight children is of significance in the aetiology of enamel hypoplasia. Such were the inconsistencies detected in the study of Grahnen et al (1969) as well as that of Mellander et al (1982).

Secondly, if even major medical conditions are considered, there is great difficulty in determining the relative importance of putative causative factors. This is because, in practically all patients who have enamel defects, most if not all important systemic causative factors are found, making it impossible to determine by multivariate analytical methods, which conditions are of significance. A couple of recent studies have demonstrated this problem. For example, Funakoshi et al (1981) examined many neonatal conditions in a group of LBW children including anaemia, hyperbilirubinaemia, respiratory distress as well as rickets and, finding that these conditions were present in nearly all the patients, suggested that all are of importance. Similarly, Pimlott et al (1985) investigated several birth parameters such as Apgar scores, admission temperatures, serum calcium levels and days to regain birth weight, but could not find any differences between the groups with enamel hypoplasia and those without enamel defects.

Also, in the study of Johnsen et al (1984), various systemic factors were considered, including respiratory distress syndrome, nutritional aspects, bilirubin concentrations and serum calcium. Although respiratory distress syndrome was reported to be the only significant condition associated with enamel defects, detailed analysis of their data showed some inconsistencies. Thus, although there was a trend for more of the children with severe respiratory distress to show enamel hypoplasia, this was not the case if enamel opacities were taken into account.

(iii) Mineral deficiency in premature infants: a possible central pathogenetic mechanism in the aetiology of enamel defects

Because of the above difficulties in determining the individual medical conditions which may be important in the pathogenesis of enamel hypoplasia, a central mechanism through which many of these systemic factors may operate was examined by Seow et al (1989a; Chapter 3, this thesis). This central mechanism is mineral loss or osteopenia, which has also been described as metabolic bone disease of prematurity (Brook and Lucas, 1985). In the controlled study of Seow et al (1989a), all children with enamel defects had greater degrees of osteopenia as measured by radiographical cortical thickness of the humerus, compared to children without defects. This study has thus shown for the first time, that there is direct relationship between decreased bone mineral stores and enamel defects.

Although previous authors (Nikiforuk and Fraser, 1981) have proposed a theory that hypocalcaemia (i.e. low serum calcium levels) may be directly responsible for developmental defects of enamel in general, it has been consistently shown by many investigators that serum levels of calcium in the neonatal period of premature infants tend to remain fairly constant even in cases of extreme calcium deficiency (Masel et al, 1982; Binstadt and L'Heureux, 1978). Thus it is unlikely that hypocalcaemia plays a major direct role in the pathogenesis of enamel defects in prematurely-born children. On the other hand, it may be hypothesized that as mineral stores are depleted in an infant to maintain serum homeostasis, calcium and

phosphorus are also prevented from entering dental structures. It may be speculated that this is achieved through homeostatic mechanisms mediated via the parathyroid hormonal axis.

That mineral deficiency may provide a central mechanism through which other systemic factors act is supported by evidence that respiratory distress syndrome, infections, hyperbilirubinaemia, anaemia, as well as intracranial haemorrhage are all associated with radiological and other evidence of decreased mineral stores (Koo et al, 1982; Greer and Tsang, 1985). These systemic conditions tend to worsen the primary factors directly responsible for mineral loss in prematurely-born children, namely, insufficiency of supply and gastrointestinal absorption of mineral substrate as well as impaired vitamin D metabolism (Tsang and Steichen, 1977; Seino et al, 1981; Koo et al, 1982).

However the existence of a central mechanism of damage to developing enamel does not exclude the possibility that individual systemic factors may also work through other known mechanisms e.g. direct cellular damage by infective agents in the case of enamel hypoplasia caused by infection.

Localised enamel defects

(i) Laryngoscopy is a source of local trauma to developing teeth

The controlled study of Seow et al (1987; Chapter 2, this thesis) has also shown that children who underwent orotracheal intubation and mechanical ventilation tended to suffer more defects

on the left-sided maxillary anterior teeth compared to non-intubated children. These defects were observed in VLBW children as none of the LBW and normal children were intubated in the neonatal period. These results thus confirm those of a previous study (Seow et al, 1984b) that trauma from the laryngoscope during the process of intubation contributes to these enamel defects.

The localization of the enamel defects to the left side may be explained by the position of the laryngoscope blade in contact with alveolar mucosa during the process of intubation. During this procedure, the laryngoscope is inserted centrally in the mouth, but the instrument is then usually moved to left of the midline in order to create room to insert the orotracheal tube in the groove along the right side of the instrument (Brooks 1982). There is little variation of this procedure even if an operator is left-handed because the laryngoscope is constructed in an universal manner.

Ideally, no traumatic force should be applied to the maxillary alveolar ridge during laryngoscopy. However in very small infants, especially those of VLBW, the mandible is so hypoplastic that it does not provide a sufficient fulcrum for lifting the anterior oropharynx and tongue in order to expose the laryngeal opening. Thus an inadvertent leverage force is sometimes exerted on the left maxillary anterior alveolar ridge, probably disrupting dental development in this region.

Further evidence that laryngoscopy is a potentially traumatic procedure is shown by the fact that the instrument can traumatise

erupted teeth (Wasmuth, 1960; Bamforth, 1963), the maxillary central and lateral incisors being most commonly damaged (Evers et al, 1967).

(ii) Orotracheal tube

Pressure from the orotracheal tube which is usually abutted against the maxillary alveolar ridge has also been suggested as a possible source of localised trauma to developing teeth. Previous authors have noted indentations of the maxillary alveolar ridges where the orotracheal tubes had been placed in LBW infants and examination of the developing incisors in these areas at autopsy had noted crown dilacerations or even tooth germ necrosis (Boice et al, 1976; Wetzel, 1980; Krous, 1980).

However, in the study of Seow et al, (1987, Chapter 2, this thesis) it is unlikely that trauma from the endotracheal tube is of significance as the infants were turned alternately on the left and right sides so that pressure from the orotracheal tube would have been evenly distributed and not localised to one side. In addition, it has also been previously shown that the children who had been intubated the longest length of time did not suffer more defects compared to those who had been intubated for only a few hours (Seow et al, 1984a).

Other oral problems suffered by prematurely-born children

(i) Delayed dental eruption

Various aspects of physical growth and development of prematurely-born children have already been studied in detail. These

include long-term studies of development of general physique, central nervous system, cardiopulmonary system and the eye (Kumar et al, 1980; Rothberg et al, 1981). Most of these studies indicate that although growth disturbances may be present for some time after birth, catch-up growth usually occurs by early childhood (Stewart et al, 1981).

However, growth and development of oral structures in prematurely-born children have not been well studied. Dental eruption in low birth-weight children was investigated by Tsubone (1962) as well as Wedgewood and Holt (1968), but conflicting results were obtained as to whether dental eruption was delayed. Other workers who investigated the age of appearance of the first tooth showed that the commencement of teething age was delayed in prematurely-born children, but eruption of other teeth was not studied (Trupkin 1974; Golden et al, 1981).

In an attempt to resolve some of the conflicting results apparent in previous literature, Seow et al (1987; Chapter 4, this thesis) investigated dental eruption in VLBW children compared with a group of LBW and a control group of NBW children. As the study was a cross-sectional one, the dental eruption status was assessed by the number of teeth present in a particular child relative to his/her age. This method did not take into account sequence of eruption and thus eliminated errors introduced if only eruption of a particular single tooth was considered. The results of the study showed that prior to the chronological age of 17 months, VLBW children had fewer teeth compared to LBW and normal children.

However, if their chronological ages were corrected to take into account their prematurity of birth, then the retarded eruption status noted in VLBW children could not be observed. Hence this study has shown conclusively that retarded dental eruption in VLBW children in the first 17 months may be attributed to their delayed biological age rather than a true delay. This fact is of relevance when considering possible systemic reasons for altered eruption in children (Sauk, 1988), as many of these conditions may accompany birth prematurity. These include endocrine disturbances such as hypothyroidism and hypopituitarism as well as bone diseases such as cleidocranial dysostosis which result in delayed eruption.

(ii) Changes in palatal shape

The softness of the bones of a prematurely-born infant makes them particularly vulnerable to abnormal moulding from external pressure. In the oral cavity, the endotracheal tube poses a particular risk for altering palatal configurations. Several studies have now shown that prolonged orotracheal intubation may lead to palatal groove formation (Nowak and Erenberg, 1984; Saunders et al, 1976); and even acquired cleft palate (Duke et al, 1976). To eliminate the risk of palatal changes associated with prolonged intubation, Erenberg and Nowak (1984) devised an appliance for stabilising orogastric and orotracheal tubes in infants. These are now commercially available.

Although these iatrogenic palatal changes have caused great concern among clinicians, a controlled investigation by Seow et al

(1985b) showed that intubated children at 2 to 5 years of age did not suffer any greater degree of palatal asymmetry compared to non-intubated children. These results indicate that whatever palatal distortions were experienced by intubated children in the neonatal period, they were resolved in later childhood, probably from growth and remodelling of the palate.

VITAMIN D-RESISTANT RICKETS

Introduction

The study of the dentition in VDRR may provide insight into the dental manifestations of many related systemic disorders which show rickets as a clinical manifestation. The main dental features observed in VDRR, i.e. multiple dental abscesses, large pulp chambers and globular dentine are also found in some acquired conditions such as odontodysplasia (Kinirons et al 1988) as well as in other inherited syndromes e.g. the tricho-dento-osseous (TDO) syndrome (Witkop et al, 1975) and the Nance-Horan syndrome (Seow et al, 1985a). In many of these conditions, the pathogenesis of the dental defects are unclear but are likely to be related to VDRR.

Possible pathogenetic mechanisms in the formation of abnormal dentine in VDRR

Improvement in the understanding of the biochemistry and molecular aspects of dentine calcification may help elucidate

possible pathogenetic mechanisms involved in the formation of abnormal dentine in VDRR. In another inherited defect of dentine, dentinogenesis imperfecta, an absence of a highly phosphorylated protein, phosphophoryn in dentine has been related to the abnormal dentine mineralization (Takagi et al, 1983; Takagi and Sasaki, 1986). While the collagen content may also be defective in dentinogenesis imperfecta (Sauk et al, 1980), it is likely that loss of the regulatory roles played by the phosphophoryns contributes to the abnormal dentine mineralization. It is tempting to speculate that the dentine defects in VDRR may also result from an abnormal composition of dentine phosphoproteins associated with the hypophosphataemia. In this regard, it has been recently noted that the crystallinity of dentine hydroxyapatite in VDRR is altered, giving rise to the possibility that there may be an associated alteration of the organic matrix (Abe et al, 1989a, 1989b). Future studies into the biochemistry of dentine in VDRR may help determine any alterations of the organic matrix.

It is equally possible that the mineralization defects in VDRR result directly from the low phosphate levels (Nikiforuk and Fraser, 1979). Many investigators have reported slow crystal growth in VDRR-affected dentine (Shellis et al 1980; Shellis 1983) as well as arrested mineralization in bone (Steendijk and Boyde, 1973). Although these authors have suggested that the effects are likely to have been caused directly by hypophosphataemia, it does not preclude the possibility that there may also be alterations in the organic matrix.

Dental manifestations occur in a broad spectrum in VDRR

The dental manifestations of VDRR have already been well described in many isolated case reports in the dental literature (Table 1.5). Most of these case reports described the classical presentations in severely-affected patients, thus conveying the erroneous clinical impression that all patients with the disease are affected to the same degree. In presenting a relatively large series of patients with VDRR, Seow and Latham (1986; Chapter 5 this thesis) showed for the first time, that in fact, the dental manifestations occur in a broad spectrum, ranging from near-normal dentitions to greatly enlarged pulp chambers and multiple dental abscesses.

To assist in diagnosis and treatment planning, Seow and Latham (1986) introduced a clinical grading system where the patients are categorised into 3 grades in order of increasing severity of dental manifestations: Grade I includes near-normal dentitions, while Grade II indicates involvement of only a few teeth. Grade III includes greatly enlarged pulp chambers, multiple dental abscesses and poorly mineralized dentine.

The above clinical grading system has been verified histologically in a further study by Seow et al (1989b; Chapter 6, this thesis). In this study, it was shown that teeth from patients with Grade I dental manifestations have only a small amount of globular dentine which did not exceed 50 percent of total dentine thickness and small interglobular spaces. Patients with Grade II severity had teeth with globular dentine involving more than half

of the dentine thickness. In Grade III severity, globular dentine extended throughout the entire thickness and the interglobular spaces appeared large.

In addition to verifying the clinical grading system, the histological study by Seow et al (1989b) also found that the appearance of prenatally-formed dentine may indicate whether the mother of the patient is affected. Globular dentine was consistently found in the prenatally-formed parts of the teeth in children of hypophosphataemic mothers who were not treated during pregnancy. In contrast, in patients whose affected mothers were adequately treated with phosphate supplementation, the prenatally-formed dentine appeared normal.

There are important clinical implications of these observations. It may be possible to determine, on the basis of the appearance of the prenatally-formed parts of the teeth, whether the mother of an affected patient is the carrier of the abnormal gene. This is particularly useful in cases where there is no previous family history of the condition and where no positive medical diagnosis has been made in the mother. In some patients, particularly females, the disease is expressed so minimally that unless medical tests are performed under stressed situations, diagnosis may be easily missed (Norman, 1987). Thus in these cases, dental histological analysis may contribute to the genetic diagnosis.

The variability in enamel defects noted among affected patients is difficult to explain. Certainly enamel defects cannot

be included as a constant finding in VDRR. In contrast, enamel hypoplasia consistently accompanies globular dentine in another inherited type of rickets, vitamin D-dependent rickets (Type I), an autosomal recessive disorder in which vitamin D activation is impaired due to low levels of alpha-1 hydroxylase enzyme produced in the kidney. It is likely that in vitamin D-dependent rickets, low serum calcium levels may be the cause of enamel hypoplasia (Nikiforuk and Fraser, 1981). In VDRR, enamel hypoplasia observed in the permanent dentition may be related to abscessed primary teeth which are extremely common in this disease.

Dental management of VDRR

(1) Prevention of dental abscesses

The prevention of dental abscesses plays a central role in the dental management of VDRR. These abscesses result from pulp exposures which occur easily due to the large pulp chambers and extension of pulp horns to the dentino-enamel junctions. If the functional surfaces of teeth are adequately capped, protection may be afforded against pulp exposures. Adhesive materials such as composite resins and glass ionomer cements may be suitable for coverage of anterior teeth but full metal crowns are advocated for posterior teeth, particularly for patients with Grade III dental manifestations. In addition to prophylactic crown coverage, patients who brux should be given acrylic splints to decrease the possibility of pulp exposures through rapid wear of the teeth (Tulloch and Andrews, 1983).

Patients showing Grade III dental manifestations require the most aggressive regimen for prevention of dental abscesses. In the management of many patients with VDRR, Seow and Latham (1986; Chapter 6, this thesis) devised a clinical routine which has been found to be extremely useful in patients with Grade III dental problems. As soon as the posterior teeth emerge, the occlusal surfaces are coated with adhesive resins as an interim measure. When the crowns of the teeth are erupted sufficiently to receive stainless crowns, the occlusal resins may be reduced to accommodate the thickness of the crowns. In addition, to eliminate the need for proximal tooth crown reduction, separating elastics may be placed to open the contact prior to crown insertion (Seow, 1984b). By these methods, the need for tooth reduction may be virtually eliminated for the placement of stainless steel crowns. Thus, the possibility of iatrogenic pulp exposures during tooth preparation is reduced.

For patients with Grade II dental problems which are confined to only a few teeth, prophylactic tooth coverage may be limited only to those at-risk teeth which may be diagnosed from radiographs.

In contrast, Grade I patients who show near-normal dentitions may need only routine preventive dental care, and prophylactic capping of isolated teeth which show enlarged pulp chambers.

Besides prophylactic coverage to prevent occlusal wear, routine prevention for dental caries is extremely important as even minimal caries can lead to pulp exposures in VDRR. Fluoride

therapy, dietary advice and oral hygiene instruction should be given regularly to all patients with VDRR.

(ii) Other management strategies

Although most clinical studies have reported success with routine endodontic procedures for abscessed teeth in VDRR, histological pictures of some Grade III teeth have shown extremely thin and poorly calcified dentine which will not withstand routine instrumentation. Thus, root perforations and fractures are definite possibilities during endodontic treatment. In some patients, extraction of some abscessed teeth may be indicated. After removal of primary teeth, consideration should be given to space maintenance.

Routine cavity preparation for restorative dentistry in patients with VDRR is fraught with the danger of pulp exposures. Because of the enlarged pulp chambers, it is important that the cavities be kept as shallow as possible. Also, cavity linings should be used routinely to protect undetected pulp exposures.

Compounding the technical problems in dental management is the problem of patient cooperation. The extensive preventive and endodontic procedures as well as ongoing multiple abscesses in patients with VDRR may tax patient cooperation considerably, particularly in the young child and various sedation techniques may be required to help patients cope in the dental chair.

HYPODONTIA AND TAURODONTISM IN THE PERMANENT DENTITION

Hypodontia of the permanent dentition represents a significant clinical problem in paediatric dentistry, with 2.8 to 10.2 percent of patients affected (Byrd, 1943; Ferguson, 1973).

Aetiology of hypodontia

Although several advances have been made in the clinical management of hypodontia, its aetiology is still not well understood. Both genetic and environmental factors have been implicated. According to Stewart et al (1982), during embryologic development, absence of tooth formation may arise from one or more of the following possibilities (1) failure of induction of underlying mesenchyme, (2) functional abnormalities of the dental epithelium, (3) space limitation e.g. in third molar region, (4) physical obstruction or disruption of the dental lamina e.g. in orofacioidigital syndrome. Acquired causes of hypodontia are similar to those associated with enamel hypoplasia, in particular, trauma or infection of developing tooth germs, and severe systemic illnesses. However, hereditary causes are by far the most common.

Although the numerous studies on oligodontia indicate that the condition shows typical characteristics of genetic disease (Neel, 1967), the mode of genetic transfer is not well understood. Current understanding suggests that hypodontia may be the result of one or more point mutations in a closely-linked polygenic system which is often transmitted in an autosomal dominant pattern, with incomplete

penetrance and variable expressivity (Graber, 1978).

However, in some cases, hypodontia may also be a form of more generalised inherited disturbance, particularly one related to ectodermal tissues e.g. ectodermal dysplasias.

Association of other dental anomalies with hypodontia

(i) Microdontia

Appreciation of various other dental anomalies occurring with hypodontia may provide further insight into its aetiology. Early work had already established that small teeth (microdontia) is commonly noted in families with hypodontia (Baum and Cohen, 1971; Keene, 1964; 1971; Hume, 1972). These observations were substantiated in a controlled study (Lai and Seow, 1989; Chapter 7, this thesis) which further showed that conical (reduced) incisors were found in 6 (8.9 percent) of 67 patients who had at least one permanent tooth missing whereas none was found in a matched, control group of patients.

The significant association of reduced teeth with hypodontia has prompted the theory that microdontia (e.g. peg-shaped incisors) is a reduced form of the hypodontic trait which is probably caused by a single gene controlling the size of individual dental units (Baum and Cohen, 1971; Garn and Lewis, 1970). However Woolf (1971) had suggested that this controlling gene is actually a gene modifier, which may itself, have a dominant mode of inheritance.

By contrast, other workers have disputed this, suggesting, instead, that hypodontia is controlled by a polygenic system. The basis of this hypothesis is based on the observation that there is poor correlation between size differences of separate components of tooth size (Rose, 1966; Roberts, 1973; Suarez and Spence, 1974; Grahnen, 1956).

A unifying aetiological explanation for anomalies of tooth number and size, recently proposed by Brook (1984), may help explain the interplay of genetic and environmental factors in the aetiology of these anomalies. Brook explained his findings using a multifactorial model having a continuous scale, related to tooth number and size, with thresholds, and suggested that numerous genetic and environmental factors affect the position on the scale.

(ii) Ankylosis

Although association of ankylosed primary molars with agenesis of their permanent successors has been described (Brown, 1981; Brearley and McKibben, 1973), there have been few controlled studies examining this observation. Brown (1981) reported that 13 (24.1 percent) out of 54 patients with ankylosed primary molars had absent premolars compared with none in 64 control patients without ankylosis. A higher association was found in the study of Lai and Seow (1989; Chapter 7, this thesis) in which 44 (65.7 percent) out of 67 patients with missing premolars had ankylosed primary molars.

The aetiological basis for the association of ankylosed primary molars and missing succedaneous premolars is unknown because

the aetiology of ankylosis and normal eruption mechanisms is still uncertain. It may be speculated that loss of controlling factors normally exerted by a developing permanent tooth germ in its vicinity has resulted in derangement of the balance between normal root resorption and replacement that is clinically manifested as ankylosis.

The strong association of ankylosis and absent teeth suggests that clinicians should be alerted to the possibility of agenesis of premolars whenever there is evidence of ankylosis of primary molars.

(iii) Taurodontism

Many sporadic cases of isolated taurodontism have been reported in the literature (Hamner et al, 1964; Lysell, 1965; Metro, 1965; Regattieri and Llewellyn, 1972; Durr et al, 1980). In some cases, familial tendencies were demonstrated (Goldstein and Gottlieb, 1973; Gamer and Zusman, 1967) and an autosomal dominant mode of transmission observed in some pedigrees (Goldstein and Gottlieb, 1973; Gamer and Zusman, 1967).

However, in many case reports, taurodontism had been observed with other dental anomalies. Robbins and Keene (1964) reported on a family showing taurodontism, dens-in-dente, odontomas, multi-tuberculated crowns of molars and microdontia. These associated defects, termed "lobodontia" were also described in the case studies of Shuff (1972) and Casamassimo et al (1978). In addition, dens-in-dente were also found in 5 percent of taurodont teeth studied by Studt (1972).

Other types of dental anomalies which have been described in association with taurodontism include some types of amelogenesis imperfecta (Winter and Brook, 1975).

Although taurodontism had been previously associated with hypodontia in case reports of some medical syndromes (Stenvik et al, 1972), the controlled study of Seow and Lai (1989; Chapter 7, this thesis) has shown conclusively that there is a high prevalence of taurodontism in patients with missing teeth compared to patients with complete dentitions. Hence in patients with agenesis of teeth, the possibility of this dental anomaly should also be checked.

Several clinical complications may result from the abnormal morphology of a taurodontic tooth. In endodontic therapy, the extensive height of the pulp chamber may create difficulties in location of root canals and subsequent problems in cleaning and obturation. These difficulties are compounded by the presence of pulp stones and unusual apical root canal systems which often accompany taurodontism (Ogden, 1988).

In fixed prosthesis therapy, a taurodontic molar may not be considered an adequate abutment tooth due to its smaller surface area which may be less resistant to lateral displacing forces compared to cynodont teeth. By the same reasoning, it may be suggested that exodontia of taurodontic molars should be easier compared to cynodont teeth. However, difficulties have been reported (Mangion, 1962).

It has been suggested that taurodontism may actually be advantageous from a periodontal aspect. This is due to the more apical location of the furcation which is thus less susceptible to be involved in periodontal disease.

General clinical management of hypodontia

Absence of teeth may result in poor aesthetics, particularly in the case of missing maxillary anterior teeth eg. the lateral incisors. In addition, malocclusion from drifting of the teeth into the spaces as well as occlusal collapse in the case of multiple missing teeth may pose difficult orthodontic and prosthetic problems.

With the introduction of newer, adhesive materials and improved prosthetic techniques, many of these clinical problems are being overcome. A multidisciplinary approach is usually recommended. For example, the rehabilitation of a patient with missing maxillary lateral incisors usually requires preliminary orthodontic movement of the adjacent teeth, creating ideal spaces to allow replacement prosthetic teeth to be inserted. The prostheses may be fixed composite resin-bonded Maryland bridges or conventional porcelain and gold bridges. Alternatively, removable prostheses such as partial or overlay dentures may be used, particularly when several teeth are missing and occlusal problems require correction.

Syndromes with hypodontia and taurodontism

Clues to the pathogenesis of a dental anomaly may be obtained by studying its occurrence in various syndromes of known aetiology or pathogenesis. Thus, because hypodontia and taurodontism are both observed in many syndromes of abnormalities of epithelial derivatives, it is likely that both these dental anomalies have a common pathogenetic origin.

The most common syndrome showing both hypodontia and taurodontism is ectodermal dysplasia, an abnormality of ectodermal derivatives which occurs in a large panorama of phenotypic and genotypic variants (Witkop 1975). Characteristic features in this group of disorders include abnormalities of skin, hair, nails and sweat glands. In addition, over 20 types of ectodermal dysplasias show hypodontia and taurodontism as associated traits (Smith, 1982; Stenvik et al, 1972; Moller et al, 1973; Barjian, 1960).

In the syndrome described by Seow (1989; Chapter 9, this thesis) both taurodontism and hypodontia were observed in a family which had characteristic diffuse palmoplantar hyperkeratosis. This association of the two dental anomalies with an obvious disorder of epithelial structure is further evidence that their origin may be related to an ectodermally-derived aberration.

In addition, both hypodontia and taurodontism have also been found in syndromes involving abnormalities of both ectodermal and mesodermal derivatives. This is the case in otodontal dysplasia, an autosomal dominant syndrome which characteristically show

microdontia, hypodontia, taurodontism and deafness (Lichtenstein et al, 1972; Levin et al, 1975). Also, in Rieger syndrome (developmental defects of the iris, cornea and anterior chamber of the eye, myotonic dystrophy, mental retardation), hypodontia and taurodontism are often found (Gorlin et al, 1978; Jorgensen, 1982).

Both taurodontism and hypodontia have also been observed in some chromosomal abnormalities. This is the case in Down syndrome which is characterized by mental retardation, myotonia, short stature, sparse hair, depressed middle third of face, cardiac and gut abnormalities as well as hypodontia, microdontia and taurodontism (Barden, 1983; Jaspers, 1981).

In addition, the Nance-Horan syndrome which is characterised by congenital cataracts, microphthalmia and anteverted pinna, also show hypodontia as a significant feature (Seow et al, 1985a). Other interesting dental findings in this syndrome include peg-shaped central incisors, anterior supernumerary teeth and taurodont molars with unusual rhomboidal crown morphology and prominent pulp horns (Seow et al, 1985a).

However, taurodontism without hypodontia has also been found in some syndromes. The most interesting of these is Klinefelter syndrome in which the degree of taurodontism has been suggested to be related to the number of X chromosomes in the cells of affected individuals (Jaspers, 1981).

FURCATION CANALS IN PRIMARY MOLARS

Accessory canals communicating from the pulp to the periodontal tissues in the region of the bifurcation or trifurcation of primary molars have considerable clinical significance in paediatric dentistry. However, studies of the furcation region, particularly of primary molars, have been relatively few.

Interest in this anatomical part of the tooth was first aroused from clinical observations that many necrotic primary molars show bone loss in the furcation area (Winter, 1962; Myers et al, 1987), suggesting possible channels of communication between the pulp and periodontal bone in this region of the root. To demonstrate this, Winter (1962) used a dye perfusion system to study by direct observation, the prevalence of patent accessory canals in the furcation region. He reported that 29 percent of 100 primary molars possessed accessory canals leading to the inter-radicular root surface, with the opening of these canals found principally on the middle third of the root surface. The above results were confirmed by Moss et al (1965) in a histological study which found that 20 percent had accessory canals entering the pulp chamber in the region of the furcation of the roots. However, both these studies were done on primary molars which were extracted for interradicular abscesses diagnosed from radiographs, hence the results may be biased.

The study of Ringlestein and Seow (1989; Chapter 10, this thesis) which showed a prevalence of 42.7 percent in 75 randomly-selected teeth, probably reflects a more accurate prevalence of

furcation canals of primary molars. Although some of the canals may be not be patent in the healthy in-vivo state due to connective tissue seals, they represent potential channels which may be opened up during pathological changes in the pulp.

Thus, through these channels, infection from the pulp may spread to the interradicular bone (Seltzer et al, 1963; Winter 1962). The destruction of furcation bone by this process represents the major cause of deep periodontal pockets in the primary dentition. On the other hand, it is unclear whether infection originating from the periodontium may affect the pulp through these channels. However, periodontal abscesses are uncommon in the primary dentition, although they may occasionally be observed around impacted foreign bodies, orthodontic bands and poorly-fitting stainless steel crowns.

In addition to infection, medications placed in the pulp chamber may also enter furcation canals to reach the inter-radicular alveolar bone, thus increasing the potential for both local and systemic toxicity. Recognition of the presence of these communication channels alerts the clinician to use only minimal amounts of intrapulpal medications.

CONCLUSIONS

The work in this thesis has contributed significantly to further the understanding of the 3 groups of developmental anomalies studied. In prematurely-born children, it was established

conclusively that the lower the birth-weight of a child, the more predisposed he/she is to develop enamel defects. Osteopenia or mineral deficiency is a likely mechanism through which many systemic illnesses cause enamel defects in prematurely-born children. Traumatic factors from laryngoscopy and endotracheal intubation are responsible for localised enamel hypoplasia observed mainly in left-sided maxillary anterior teeth. However, although enamel defects are common oral complications of premature birth, true retardation of dental eruption is not observed.

The dental manifestations of vitamin D-resistant rickets occur in a broad spectrum which may be clinically as well as histologically graded from I to III in order of increasing severity. Such a grading system has significant clinical value in determining the risk of an affected patient to develop dental abscesses and thus the need for dental protection.

The strong association found between hypodontia and taurodontism may indicate a common origin for both these dental anomalies. This hypothesis is substantiated by the clinical observation that in many medical syndromes, particularly those with abnormalities of ectodermal derivatives, both hypodontia and taurodontism are found.

Work in my research unit continues to focus on the broad theme of developmental dental anomalies. In this regard, additional studies have been completed since the submission of this thesis. In the area of prematurely-born children, light and electron

microscopic investigations of exfoliated teeth from these patients have shed light on the nature of the enamel defects at the ultrastructural level (Seow et al, 1990; Seow and Perham, 1990). In the area of vitamin D-resistant rickets, assessment of the degree of dentine mineralization at the ultrastructural level, using a novel objective method, has confirmed the validity of the grading system of the spectrum of dental manifestations (Seeto and Seow, 1990). Of further interest is my recent finding that conventional medical therapy does not significantly influence dentine mineralization in VDRR (Seow, 1990).

Clinical studies form an important component of the total research effort in dentistry. While laboratory-based dental research can offer basic understanding of the aetiology and pathogenesis of disease processes, clinical research programmes are needed to bring the benefits of this increased understanding to the chairside. Furthermore, clinical research can identify and clarify problems encountered at the chairside so that these problems can be brought to the laboratory for further investigations. It is hoped that the clinical research reported in this thesis may have contributed in some way to these two important processes of dental research.

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